Mutations in Breast Cancer Exome Sequences Predict Susceptibility to Infections and Converge on the Same Signaling Pathways

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ABSTRACT: Many mutations in breast cancer exome sequences alter susceptibility to infections. An exhaustive analysis of all the mutations in exomes from 103 breast cancer cases found that more than 1,000 genes have a published association with some kind of infection, including all known tumor viruses. Altered susceptibility to infection was identified as a common thread connecting breast cancer mutations in genes traditionally classified as coding for diverse functions, including cell immunity, cell architectural barriers, stromal interactions, cell adhesion, DNA damage responses, translation, cell cycle control, metabolism, homeostasis, transport, and neurosensing. Infections and mutations can both contribute to cancer because they deregulate the same pathways. In many cases, infections make a contribution to cancer that is either known or biologically plausible. Interventions may be possible to prevent occult infections from cooperating with mutations to cause further cancer, metastasis, or other complications. The emerging list of infection–gene mutation associations is readily scalable to routine testing of large human data sets.

KEYWORDS: breast cancer, infection, viral cancer, cancer genome, cancer infection, breast cancer mutation

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Introduction

Lesions are thought to become malignant because mutations accumulate over long periods to disable or deregulate essential cellular controls. Some mutations may activate proto-oncogenes to become uncontrolled oncogenes, and other mutations may inactivate tumor suppressor genes. About 15%–20% of cancers are known to be caused by tumor viruses or other infections.[1] Infectious and noninfectious cancers are considered as separate diseases and are even studied in separate disciplines. Relationships between infections and cancers have produced some notable successes, such as the ability to prevent some cancers of the cervix and the liver. In other organs, associations between a single individual infection and cancer have been difficult to reproduce. For example, breast cancers have been associated with very different infections including retroviruses (mouse mammary tumor virus [MMTV] and human endogenous retrovirus [HERV]), a large double-stranded DNA virus (Epstein-Barr virus [EBV]), and a small double-stranded DNA virus (human papilloma virus [HPV]). Results linking any one of these infections to breast cancer are contradictory and difficult to reproduce.[2] Asymptomatic infections have spread tumor viruses through the population so that virtually everyone has been inoculated with tumor viruses such as EBV and HPV. Tumor viruses have been widely reported in normal breasts, so if viruses cause cancer, most women should probably develop breast cancer.

One reason this does not occur is because breast cancers may require mutations in genes that lead to compromised immunity.[3,4] Gene mutations that deregulate the immune system, cellular architecture, or underlying metabolic support create errors in the signals that prevent viral infection and in signals that maintain resident tumor viruses in a latent state. In addition, some bacterial infections may cause chronic inflammation with continual cell proliferation in the presence of mutagens or the infecting bacteria may even release carcinogenic metabolites.[5–7] Under these scenarios, no matter what the infectious agent, mutations that damage host cell–protective mechanisms or normal cell functions would increase risks for cancers.

In breast cancer, gene mutations can alter the ability of the immune system to control cancer-causing infections in multiple ways and high percentages of mutations can be linked to damage to protective signals.[3,4] Some host mutations interfere with signals that cells are under attack and that protective boundaries have become abnormal. Signals connecting innate and adaptive immunity may not work properly. Communication between cells and the extracellular matrix may be damaged by mutation. Changes in cellular morphology and metabolism are needed to convert normal cells into cancer or viral factories. Mutations in genes encoding proteins essential for transcription, mRNA splicing, or translation can facilitate or inhibit viral takeover.

Essential signals to metabolism underlying pathogen clearance and the intracellular environment may be abnormal or become abnormal because of mutations. Mutations may alter a gene product enough to disable its normal host cell function but not enough to prevent a pathogen from using it anyway.

Do gene mutations in breast cancer cells affect the same signaling pathways as pathogens? Do different breast cancer gene mutations cause signaling errors that alter responses to different infections? Because each breast cancer likely has damage to different signals, are cancers in different patients likely associated with different sets of infections? Would a comprehensive search for infections in breast cancer cells or their surroundings find that cancer cells are predisposed to infections? Do viruses or other infections contribute to cancers that are not now classified as infectious in origin? To explore these questions, 4,985 exome mutations in 3,807 different genes from 103 different breast cancer patients were examined in detail to determine whether cancer mutations systematically associate with infections, especially infections known to cause cancer.

Materials and Methods

Data used. Breast cancers blindly used for analysis were from publicly available data for sporadic breast cancers.[50] As previously described,[3,4,49] studies selected were heavily weighted for ductal cancers because ductal cancer is the most common form. The whole-exome sequences came from 103 matched sporadic female breast cancer/normal pairs from Mexico (54 tumors; median age, 54) and Vietnam (49 tumors; median age, 48).[50] Eighty-seven of these 103 sporadic breast cancers were invasive ductal. Sixteen cancers from the group were tubular, medullary, mucinous, mixed, lobular, and ductal carcinoma in situ (DCIS). Over 60% of the breast cancers were stage II, but about 20% were stage III. Eight (15%) of the cancers from Mexico and three (6%) from Vietnam were stage I. Nine (17%) of the breast cancers were stage 0 (DCIS). These breast cancer exomes had 4,985 candidate somatic gene mutations that involved 3,807 different genes.[50] Twelve women from Vietnam were postmenopausal and the remaining 27 were premenopausal. The menopause status of the women from Mexico is not known but 21 were younger than 50 years. The ages of the women ranged from 31 to 92.[50] Lists of oncogenes and tumor suppressors were taken from lists compiled for the CancerGenes website.

Databases used and methods of functional analysis have been previously described.[3,4] Briefly, the functions of each testable gene with an exome mutation were determined by searching through all the information published about the gene on PubMed, Google scholar, and/or The Online Mendelian Inheritance of Man. Many original papers were also consulted. Functional analyses were limited to the most recent 100 references published. After the normal function of a gene was determined, further searches tested the name of the gene against "infection, virus, bacteria," etc. In many cases the relationships among genes and infections could only be found by studying publications describing the life cycle of candidate microorganisms. Based on similarities to retroviruses, retrotransposons were tentatively classified as infectious in origin. About six retrotransposons were associated with mutations and had no significant effect on the results. An initial classification of genes related to innate immunity was obtained by comparing genes listed in innate immune databases.[57–59] Statistical analyses were done with Excel and StatsDirect.

Results

Mutations focus on immune signaling. Many different signaling pathways are affected by mutations in different breast cancers but a common thread is that they alter responses to infection. In many cases, the altered responses are to infections known to cause cancer. This is based on studying 4,985 mutations involving a total of 3,807 genes in 103 sporadic breast cancer exomes. Figure 1 is a pie chart showing the numbers of mutated genes placed into broad functional categories. Of the 4,985 total exome mutations, most of them (3,427 mutations) had some relationship to signals essential for immunity or for structural and architectural barriers needed to prevent or sequester infections.

Of the 3,807 different genes with mutations, only 2,947 could be tested (Fig. 1). Among these 2,947 genes with mutations are 1,077 different genes (36.5%) that are known to respond to some infection. In all, 774 mutations occurred in genes encoding products for more diverse cellular functions: homeostasis, metabolism, hormonally mediated phenomena, cell cycle, replication, transcription, translation, etc. Among these 774 mutations, at least 287 were associated with some kind of infection.

Table 1 shows how the mutations are distributed among the most prevalent infections. There are many opportunities for associations among mutations and known cancer-causing microbes. All known cancer-causing microbes are represented among these infections. Human immunodeficiency virus (HIV) appears most frequently, but this may merely reflect the intensity with which AIDS has been studied. Nonetheless, in the presence of a damaged immune system, associations between gene mutations and HIV infection probably raise the risk for AIDS-defining malignancies such as Kaposi sarcoma, non-Hodgkin lymphoma, and cervical cancer. Other cancer causing viruses including EBV, hepatitis B virus (HBV), hepatitis C virus (HCV), and HPV are all represented about equally in Table 1. *Helicobacter pylori* occurs roughly half as often; human herpes virus type 8 (HHV-8), Dengue virus (DENV), and human T-cell leukemia virus (HTLV) slightly less than that. Associations with other viruses such as human cytomegalovirus (HCMV), influenza A virus (IAV), and with bacteria, mycobacteria, fungi, parasites, and prions. There were a few infections associated with mutations in transposon and retrotransposon genes (Tables 1 and 2). (Gene symbols and microorganism abbreviations are inserted before the author contribution section of this paper).

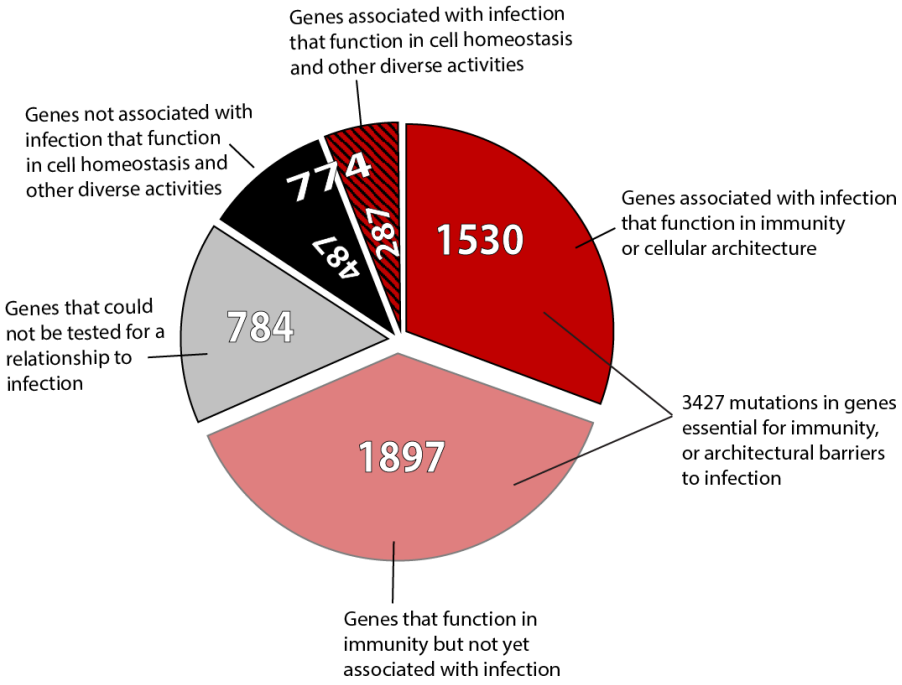

Figure 1. Distribution of 4,985 mutations in 103 breast cancers including categories with relationships to infections. The numbers within the pie slices indicate the numbers of gene mutations in the category represented.

To illustrate how this information might translate into actionable interventions, 41 demonstration breast cancers were selected at random from the list of 103 breast cancers. A random number generator was used to prevent bias or unwitting cherry-picking of the data. At the 90% confidence level, the 41 breast cancers are sufficient to show that multiple infections are universal and typical of every one of the 103 sporadic breast cancers. Many genes encode proteins with multiple functions, so seemingly disparate signals modified by infection often have some connection to immune signals, support of immune responses or cell architectural barriers, or to a variety of other functions. All these processes change susceptibility to groups of infections. All breast cancers in Table 2 have mutations associated with multiple infections, including viruses, bacteria, fungi, parasites, and prions.

Table 1. Most prevalent infection susceptibilities altered by mutation in 103 breast cancers.

INFECTION	NUMBER OF GENE MUTATIONS IN 103 BREAST CANCERS ASSOCIATED WITH INFECTION IN COLUMN 1
HIV	341
HCV	283
EBV	281
HPV	271
HBV	228
(H)CMV	145
H. pylori	122
Bacteria, *pseudomonas*, *E. coli*, *mycobacteria*, *MTb*, *listeria*, *S. aureus*, *salmonella*	253
HHV-8/KSHV	109
HTLV-1	83
DENV	78

In some breast cancers, mutations may favor a single infection. Patient BR-M-116 had 15 mutations and BR-M-045 had 8 mutations that altered the risk from EBV infection. BR-M-045 had seven mutations that altered HCV risk. BR-M-123 and BR-M-105 had 12 and 7 mutations, respectively, that altered the risk from carcinogenic HPV infection. BR-M-105, BR-M-116, and BR-V-002 had seven mutations that altered risk from HHV-8 infections (Table 2). Mutations that alter risks for bacterial infections were also found in the breast cancers and must represent a substantial burden. Individual single mutations in Table 2 were often associated with multiple infections.

Associations between breast cancer mutations and infections are biologically plausible. To determine whether there were biologically plausible relationships between breast cancer mutations, infection, and known signaling pathways, mutations were tested against multiple known signaling pathways. As examples, immune[8–12] and protein translation signaling pathways[13–15] in response to infections are diagrammed in Figures 2 and 3, respectively. Red boxes show breast cancers that have mutations for genes encoding some of the steps in the pathways with the assumption that virtually all mutations

Table 2. Forty-one randomly selected sporadic breast cancers examples showing that all breast cancers tested have mutations associated with infections, many known to cause cancer.

NO.	RANDOMLY SELECTED PATIENT	INFECTIONS ASSOCIATED WITH MUTATIONS/[NUMBER OF MUTATIONS WITH EACH INFECTION IF >1]	MUTATED GENES ASSOCIATED WITH INFECTIONS	NUMBER OF MUTATIONS IN PATIENT'S EXOME
1	BR-M-027	AAV, ADV, AEV, ASFV, *Aspergillus nidulans, C. trachomatis/psittaci[4]*, CPXV, DENV, EBV[2], EV71, *h pylori*, HBV[3], HCMV [2], HCV[3], HERV-E, HHV-8, HIV-1[7], HPIV, HPV[2], HSV[2], HTLV-1[2], IAV, JCV, LCMV, *Leshmania*, *mycoplasma,* nematode infection, PICV, *plasmodium falciparum*, prion infection scrapie, RABV, reovirus, rhinovirus, RSV[3], *S. Typhimurium*, SFV, SIV, *T. gondii, T. cruzi,* VACV, WNV [mice]	EGFR, GAP43, IL13RA1, TYK2, BRCA1, CRTC2, ENTPD1, FOXO4, PLK3, C3AR1, DNAH17, FSCN1, HIST1H1A, MID1, PREP, CWC25, INSR, LZTS1	68
2	BR-M-028	CVB3, DENV, EBV, HBV[2], HIV-1[5] alpha herpesviruses, HPV, IAV, LCMV[2] [mice], *Leshmania, Listeria, MTb*, NDV, *plasmodium, pneumoccus,* pneumovirus (mice), RSV[2], *Salmonella*, SeV[2], *Shigella*, Sindbis virus, VSV	IL27RA, KIF1A, NACA, NLRP4, OAS2, PDS5A, PIK3CA, PLEC, SEC14L1	31
3	BR-M-037	ADV[6], *Aspergillus fumigatus,* Borna disease virus[rat], *Borrelia spirochetes, BHV-1[3], Burkholderia cenocepacia, c.jejuni, candida, canine parvovirus, chlamydia, clostridium,* CV/CVB3, CMV[2]/HCMV[3], CVB3mice[2], DENV[6], EBOLA[3], EBV[14], ECHO30, *E. coli, Francisella tularensis,* GM negative bacteria[2], Hantaan Virus, HBV[9], HCV[16], HERV[2], HEV, HHV-8, HIV[22], HPV[5], *H. pylori*[4], HSV-1/2[8], HTLV-1[3], IAV[6], JEV[4], LCMV, Lung infections, MTb., Marburg virus, MV[2], MCPyV, MHV-08, MMTV, MRSA, HTLV-1, MTb, MHV68, MV, NDV, *N. meningitides, N. gonorrhoeae,* paramyxovirus[3], plasmodium[3], Poliovirus, poly-microbial sepsis, BKV, prion Infection, PV, rabies, recurrent infections, Reovirus, rotavirus, RSV[3], RVFV, SV-A, *S. Typhimurium[2]*, *S. aureus, S. aureus (mice)*, SeV, *streptococcus[2]*, SV40, Swine fever virus, *T. gondii*, TBEV, TGEV (pigs), VACV[4], VSV, VZV[2], WNV[3], *Yersinia*	APEX2, APLP2, BCL6, CCDC40, CD22, CENPJ, CFB, DDB1, DHX29, DIAPH1, DST, EEF2K, EIF3A, ERCC5, ERVFRDE1, EYA1, FOXF1, GEMIN5, GPX4, GSS, GTF2E1, HJURP, HLA-A, IGF2BP2, IL15RA, IL21R, IRAK2, KDM3A, LYST, MAD1L1, MAGI3, MAP2, MAP3K1, MBP, MGAM, MIPEP, MUSK, NCOA2, NCOR1, NR4A2, OPRM1, PGK1, PIGP, PLEC, PLXNA1, PRDM2, PSME3, ROBO3, RYR2, SH3GL2, SIN3B, SLA2, SLC1A6, SLC30A1, SLC38A5, SNAPC2, SUPT5H, TEC, TF, TFAP2C, TLR3, TNNC2, TRIO, TTN, UBR1, XPC, YES1, ZNF136, ZNF652	213
4	BR-M-038	*Aspergillus, Borrelia spirochaetes, candida, coagulase-negative staphylococci,* DENV, EBV, HPV[3], *H. pylori*, HSV-2, IAV, parvovirus B19, polymicrobial sepsis, scrapie (mice), viridans group *streptococci*	MST1, PRDM16, RTEL1, SMO	21
5	BR-M-045	ADV, *Anaplasma phagocytophilum*, bacteremia with enteric pathogens, BK polyoma virus, *Campylobacter jejuni, candida, chlamydia*, CMV, Coxsackievirus A9, Coxsackievirus, dental abscess, DENV, dsRNA viruses, EBV[8], *E. coli*[2], Gram positive bacteria, HBV[4], HCMV[5], HCV[7], HCV-HIV co-infection, HHV-8[3], HIV-1[6], HPV with HIV-1, HPV[3], *H. pylori*[2], HSV-1[3], HTLV-1[2], IAV[3], *Legionella pneumophila, Listeria monocytogenes[2]*, MTb[2], Marek's disease virus, MCPyV, MHV-08, Molluscipox virus, *MRSA*, MHV68, *Mycobacterium assiliense*, picornoviruses, *plasmodium*[2], *Pneumococcus*, poliovirus, polyoma virus[2], Positive strand RNA viruses, *pseudomonas aeruginosa*, pseudo rabies virus, PV, rabbit myxomavirus, Rhesus rhadinovirus, rotavirus, RSV[2], RVFV, *S. aureus[2]*, *Salmonella, sepsis. Staphylococcus, dermatophyte fungi*, VacV[2], VSV[2], VZV[2], WNV	ADAD2, ARAP2, BAMBI, BLZF1, CYBB, CYP1B1, DUOX2, ERO1LB, ESRRG, FCRL5, FCTL5, FLG, GRM1, HSPH1, IDE, IL31RA, IRAK4, KDM4A, LDLRAP1, LRP1B, MED13, MYBBP1A, NHS, PDE2A, PIKFYVE, PKHD1, POLR3A, PTPRN, RAB6A, RNASE4, RPN2, RRM2, RYR2, SFTPC, SKP1, SMG5, SP1, SRMS, STAM2, TAPBP, TGFBRAP1, TP53, ZNF7	141
6	BR-M-048	*Aspergillus fumigatus, clostridium*, DENV, dsRNA virus, EBV[2], HCMV, HCV[3], HHV-8, HIV-1[3], HIV-1, HPV[3], HSV-2, MHV68, *N. gonorrhoeae, plasmodium,* prion infection, RSV, *Streptococcus B*	CYP21A2, DNAH3, FOXO1, GRIN2D, ITSN2, MLXIPL, NCOR1, PIGM, PRDM5, PRKRIR, USP12	14
7	BR-M-050	EBV[3], *chlamydia[2]*, EBV, HTLV-1, *S. typhimurium[2]*, *T. gondii*, CVB3 (mice), EBV[2], HBV[3], HCMV[2], HCV[6], HIV-1, HPV[2], HTLV-1[2], IAV, MMTV integration site, mycobacteria, PV, retrotransposon, RSV, *Yersinia*[2]	MAP3K1, MED14, PIK3CA, PTEN, EPX, HNRNPU, HAS1, MAML2, WNT10A, NOLC1, UTP14	32
8	BR-M-055	ADV, DENV[3], *E. coli* meningitis, EBOLA, EBV[3], *giardia muris*[2], *H. pylori*, HPV, HBV[3], HCMV, HCV[3], HERV, HHV-8[2], HIV-1[3], HPV, HSV-1[2], HEV71[2], IAV, *Listeria monocytogenes*, Marburg virus, Marek's disease virus (poultry), *plasmodium*, PV, recurrent sino-respiratory infections, *Salmonella enteritidis* [chickens], MTb?, VACV	IFI16, PIK3CA, FAF1, HDAC9, POU2F1, GGA1, HIST1H1C, MLL2, RPGR, DDX20, GAA, GLUD2, RNGTT, SRRM2, SIRT2	93

9	BR-M-083	*Acinetobacter baumannii, aspergillus, Borrelia burgdorferi, Burkholderia, pseudomallei, C.difficile, Clonorchis sinensis, Coxiella burnetii,* DENV, *E.coli,* EBV[2], *endotoxemic shock, Entameba histolytica, fungal pathogenicity, GM negative bacteria, HBV[3], HCMV, HPV[5], H. pylori,* hMPV, IAV, *L. monocytogenes, MTB, mycobacteria, m. bovis,* norovirus, *P. aeruginosa,* PV, RSV. RV14, *salmonella [2], S. aureus, Shigella, staphylococcus, Strep. Pneumoniae, T. gondii, T. spiralis, Trichuris muris*	NOD 2, PIK3CA, UACA, GOLGA2, JUP, MUC2, SHH, CAD, SLC6A8	22
10	BR-M-105	AAV, *aspergillus*, bocavirus, *candida*, EBV[3], *H. pylori,* HBV, HCMV, HCV[2], HHV-8, HIV-1[2], HPV[7], HSV-2, HTLV-1[2], JCV, MCPyV, *P. aeruginosa*, parvovirus B19, RSV, RVFV, sindbis virus, *staphylococcus [2], streptococci viridans group*, SV40	ATM, BCOR, CYP2C8, DDX11, DNAH8, FBXL2, JUP, MKI67, PRDM14[4], PRDM16, WWOX	32
11	BR-M-116	ADV[4], *Aspergilla [2]*, Bacteremia[2], BKPyV, chlamydia, CVB3, CVB4, DENV, *E. coli*, EBV[15], EMCV, *F. tularensis*, feline sarcoma virus, Gamma herpesviruses, GM negative bacteria, *H. pylori[4],* HBA, HBV[8] HCMV[5], HCV[5], HCV, HERV-E, HHV-8[7], HIV-1[8], HPV[5], HSV-1[4], HTLV-1, IAV[5], *M. leprae[2], mycobacteria*, oral bacterial infections, *plasmodium,* PV, RSV (bovine)[2], Rubella, *s. aureus*[2], *S. pneumoniae, S. typhimurium[2],* sepsis, SV40[2], *T. cruzi,* TGEV, VSV[4]	ARID2, BMF, BRAF, BUB3, CLDN 6, CPS1, DMD, DOT1L, DST, DYNC1H1, DYNC1I1, DYRK1A, EDNRB, EPRS, ERAP2, ERAS, EXT1, FAN CF, FBXO 48, FES, GBP1, GLT6D1, H2AFX, HTRA2, HUWE1, IGF1R, ITIH4, LMAN1, MCHR1, MLL, MSRA, NEBL, NOXO1, PDK1, PIGR, PIK3CA, PKD1, POU2F1, PPP2R4, PTPRD, REV3L, RIOK3, SOS2, TFF1, TRABD, USP22, VPS13B, ZMYND11	145
12	BR-M-120	*Clostridium perfringens, Campylobacter jejuni C. difficile, Clonorchis sinensis,* EBV, *E. coli[2], Entamoeba histolytica,* HBV[2], HCMV, HCV, HHV-8, HIV-1, hMPV, HPV[3], *h. pylori,* HSV-1[2], IAV, *L. monocytogenes, P.aeruginosa,* RSV, RV14, *sepsis, S. typhimurium[2], shigella, T. spiralis*	ADAMTS7, CLDN14, IRF2, KALRN, MLLT4, MNDA, MUC2, PIK3CA, SCAMP3, SEC24A, SLC9A2, SP100	36
13	BR-M-121	*Anaplasma phagocytophilum, aspergillus, C. difficile, candida,* coagulase-negative *staphylococci*, EBV[4], ERVK, HBV, HCMV[2], HIV-1[4], HPV[3], HSV-2, oral bacterial infections, parvovirus B19[2], Reovirus, Rubella virus, *salmonella*, SV40, viridans group *streptococci*	CNOT1, CRYBA2, EIF3K, GLT6D1, MACF1, NCOA4, NES, NPHS2, PIK3CA, PRDM16, RARG, RECK, RFC4, STARD3, TNC, TXNRD1, ZNF652	40
14	BR-M-123	Borna disease virus [rat], *C. trachomatis,* DENV[2], EBV[2], filovirus, *F. tularensis*, fungi, Gm positive infections, *H. pylori*, HBV[2], HCMV[2], HCV[3], HHV-8[2], HIV-1[4], HPV[12], HTLV-1, IAV[4], *L. monocytogenes, MTb./mycobacteria[2]*, MCPyV, microbes and viruses, *P. falciparum*, prion disease [kuru], *P. aeruginosa*, RSV-1, Rubella virus, RVFV, sepsis [2], *T. cruzi*, VaCV, VZV	CD6, CSF3R, DLL1, FCRL6, FOXA1, HPS4, NCR3, PCGF2, PCGF2, RFXP3, S1PR3, SLCA16, STMN2, TP53, XRCC2	59
15	BR-M-154	ADV, DENV, gram negative bacteria, HBV, HCV, HIV-1[3], HSV-1, HTLV-1, IAV[2], JEV, *M. pneumoniae*, MHV68, Positive strand RNA viruses, e.g. HCV, reovirus, SeV, VACV[2]	CLSTN1, DDX21, ERGIC3, GREB1, HDAC5, IFIT2, RAB11FIP1, SFRS1, SMG5, TAS1R2	32
16	BR-M-155	Bacterial sepsis, *C. albicans, chlamydia*, EBV[2], Flovirus, *h. pylori*[2], HBV[2], HCMV[2], HCV[5], HIV-1[3], HPV, HSV-1[2], *L. monocytogenes,* MMTV[3], *Paracoccidioides brasiliensis,* polyoma, *S. aureus, schistosomiasis [mouse], T. gondii*	AKT1, CBFB, DST, EIF2A, FDPS, FGF3, FIZ1, HTATSF1, IGF1, IL12A, NPC1L1, WNT2	42
17	BR-M-158	*C. difficile*, DENV, Ebola, EBV[2], fungal allergic airway disease, HBV[4], *L. monocytogenes, S. aureus*, septic shock, SV40, WNV	FANCI, GAS6, INSR, NCOA4, NLRP3, PIK3CA, VPS13D	25
18	BR-M-167	*C. difficile. Chlamydia, Clonorchis sinensis, Cryptosporidium, E. coli[2],* EBV, *Entamoeba histolytica, fusobacterium nucleatum, H. pylori[2],* HBV[2], HCV[2], HIV-1, HPV[2], HSV-2, *L. monocytogenes, Listeria, Neisseria,* polyoma, *Rickettsia, RV14, S. dysenteriae, S. typhimurium, shigella[3], Staphylococcus,* VACV	AKT1, CBFB, CTTN, ERCC4, GRIN2A, MUC2	23

(*continued*)

Table 2. (*Continued*)

NO.	RANDOMLY SELECTED PATIENT	INFECTIONS ASSOCIATED WITH MUTATIONS/[NUMBER OF MUTATIONS WITH EACH INFECTION IF >1]	MUTATED GENES ASSOCIATED WITH INFECTIONS	NUMBER OF MUTATIONS IN PATIENT'S EXOME
19	BR-M-169	ADV, *C. difficile, Candida albicans, Clonorchis sinensis,* DENV[2], *E. coli*, EBV, *Entamoeba histolytica*, HBV[2], hMPV, HPV[4], *L. monocytogenes, P. aeruginosa,* RV14, *S. typhimurium, shigella, Streptococcus pneumoniae, T. spiralis, Y. pseudotuberculosis*	CFHR4, IRS4, MUC2, PIK3CA, UBR4	21
20	BR-M-172	ADV, DENV[2], gm negative bacteria, *H. pylori*, HBV, HCMV[2], HCV[2], HIV/HCV co-infection, HIV-1[4], HPV[4], HSV-1[3], Intracellular bacteria, *P. aeruginosa, P. falciparum*, polyoma, Puumala hantavirus, SIV, surgical site infection, *Trypanosomes*	ALDH1A3, ATRX, CBFB, GP6, HGF, HUWE1, JAK2, NLRP7, PAX3, PZP, SEPSECS	29
21	BR-M-186	EBV, HBV, HIV-1[2], HPV, *P. aeruginosa*, Positive strand RNA viruses	FCN1, RAB7A, GAST, SMG7	18
22	BR-V-002	*Acinetobacter* [MDR], ADV, ADV5[adenovirus 5], amniotic bacteria, *Anaplasma phagocytophilum*, DENV, *E. coli* animals, EBV[5], gram negative bacteria, *H. pylori*[2], HBV[2], HCMV[4], HCV[6], HHV-8[7], HIV-1[7], HPV with HIV-1, HPV[5], HSV[4], HTLV-1[3], IAV H1Nx/IAC, IAV, IBDV, legionella virulence, M. Avium Subsp. Paratuberculosis, MCPyV, MLV, MRSA, *mycoplasma*, NiV, polyoma virus, *pseudomonas* [MDR], Reovirus, some retroviruses, rhinovirus, RVFV, *salmonella, shigella, T. cruzi*	A2M, APEX1, BIRC6, BPI, EIF2AK3, EIF4G3, ITSN2, KL, MDC1, MED28, MMP15, MYB, NPLOC4, NR4A2, OSBP, PACS1, PDE7A, PSORS1C1, RPS6KB1, SALL2, SDHA, SON, SP100, SPEN, SRRM2, TP53, VAMP4, VDAC2, YTHDC2, ZFX	98
23	BR-V-007	Alpha herpes viruses, bacteremia[enteric pathogens], EBV[2], *H. pylori*[3], HBV[2], HCMV[3], HCV[3], HHV-8[2], HIV-1, HPV with HIV-1[2], HPV, Marek's disease virus, MCPyV[3], MTb, *P. aeruginosa*, RVFV[2], sepsis	DDX47, FLT1, PON1, PKHD1, RREB1, TP53	23
24	BR-V-012	*Aspergillus, B. anthracis, bacteroides fragilis, chlamydia trachomatis,* DENV, *E. coli*, EBV[3], *H. pylori*, HBV[3], HCMV, HCV[2], HHV-6, HHV-8[2], HIV-1, HIV-1/SIV[2], HPV[3], HPV with HIV-1, *H. pylori*[2], HTLV-1, IAV[2], HCV, HBV, *leptospira interrogans*, Marek's disease virus [poultry], MCPyV, Mucor fungi, murine encephalomyocarditis, *mycoplasma[2], N. gonorrhoeae*[2], Puumala hantavirus, rotavirus?, RSV, RVFV, *S. aureus,* spirochetes, *T. gondii*	BEST3, GH1, GRB14, ITGA11, KIAA0226, MUC5B, NRXN1, RNF39, ROR2, SEPT6, TP53, USP22	30
25	BR-V-013	Flovirus, HBV[3], HCMV, HCV[2], HIV-1, HSV-2, HTLV-1, JEV, *T. gondii*	CAPRIN1, CRTC2, FNDC3B, GRIN2A, HSPBP1, MYT1, NPC1L1, STXBP5L	32
26	BR-V-014	AAV, ADV, AEV, ASFV, baculovirus, BK polyomavirus, CHIKV, *chlamydia*[4], CPXV-WR, *cryptosporidium*, CVB3[3], CVB4, DENV, *E. coli*[2], EBV[3], EV71[3], foamy virus, gram negative bacteria, *H. pylori*[2], HBV[4], HCMV[3], HCV[4], herpesviruses, HHV-8[2], *H. influenzae*, HIV-1[4], HIV-1 maternal fetal transmission, HPIV, HPV[4], *H. pylori*, HSV, HSV-2, HTLV-1[2], IAV, influenza, JEV, *K. pneumoniae*, Leshmania major, *M. bovis*, MCPyV, HPV [with HIV-1], *mycoplasma*, *P. aeruginosa*, PICV, *P. falciparum, pneumococcus*, PV, Polyomavirus, Reovirus[2], rotavirus, RSV, RV, RVFV, *S. aureus, salmonella, Schistosomiasis mansoni,* SFV, SV40, *T. cruzi[2], T. gondii,* VACV[2], Venezuelan equine encephalitis virus[VEEV], *vibrio parahaemolyticus,* VZV[2], *Y. pestis*	B3GAT3, BUB3, CNTN2, DMD, DNAH6, EGFR, EIF4G2, EIF5, FLNC, HS3ST3A1, HSPA8, IRS4, KIT, MAPK1, NEDD4L, OXR1, PARP12, PPP3R2, REV3L, SLC15A1, SULT2B1, TAS1R3, TNPO3, TP53, TRAF3IP3	68
27	BR-V-015	EBV, HBV, HCV, HERVK, HIV-1, HPV, IAV, *S. aureus*	LOX, PIK3CA, STAU1	15
28	BR-V-016	ADV[2], bacteria, *Borrelia burgdorferi* [Lyme disease], CVB3, EBV, *H. pylori*[2], HBV[2], HCV[2]/oncornavirus, HERV, HHV-8, HIV-1, HPV[2], *H. pylori*, HSV-1, MTb, Rauscher leukemia virus, *salmonella*, SARS, *S. aureus*, sepsis[2], SeV, SV40	AKR1C3, AKT1, C15orf2, DAAM1, FLNC, HIST1H3B, PDXK	25
29	BR-V-019	CVB3[mice], HBV, HCV, HIV-1[3], HPV[3], HTLV-1, *Listeria*, MCPyV, RSV, Sepsis	SMARCA4, ELMO2, GATA3, PROKR1, ARHGAP21, MLL4, TTN, UBE4A, TTF2	35
30	BR-V-022	*B. fragilis, Bordetella pertussis, C. botulinum,* HPV, CVB3[mice], EBV[2], *H. pylori*[2], HBV, HBV[2], HCMV, HCV[4], herpesviruses, HHV-8, HIV-1, HPV with HIV-1, *H. pylori*, IAV[2], Junin virus, MCPyV, parvovirusB19, RVFV	CDH1, CVB3[mice], HRH1, LRP1B, MACF1, MAP4K3, SHOX2, TP53, TRABD, USP11	61

31	BR-V-028	ADV, BLV, *Bordetella pertussis, Borrelia burgdorferi, chlamydia trachomatis*, DENV, *Enterococcus faecalis*, GM neg bacteria, *H. pylori*, HBE, HBV, HCMV, HCV[4], HVS, HIV-1[2], HPV[3], HSV-1[3], HSV-2, HTLV-1, IAV, JCV, JEV, Molluscipox virus, mouse gamma herpes, MRSA. MTb, *P. falciparum, P. aeruginosa, S. aureus, Schistosoma mansoni,* SEV, *streptococcus pyogenes, T. cruzi, tinea corporis,* VSV, WNV[2]	ATF6B, DSE, FLG, GPNMB, GRIN2B, HRH1, ITGAX, LRIG1, MECP2, NOTCH2, RAB13, SLC38A5, ZNF217	49
32	BR-V-030	Baculovirus, *cryptosporidium, E. coli,* EBV, HBV, HCMV, Hendra virus, HHV-6, HHV-8, HIV-1[3], *m. pneumoniae,* NiV, *S. aureus,* TMEV, *T. brucei*	CTNNA3, ELN, EPHB2, GALC, HYAL1, KLK8, NCOA3, NSMAF, SLC15A1	40
33	BR-V-031	*C. albicans, chlamydia,* DENV, EBV[4], *H. pylori[4]*, HBV, HCMV[2], HCV[3], herpesvirus saimiri [HVS], HERV, HIV-1[2], HPV, HSV-1, HSV-2, IAV, JCV, *L. monocytogenes, MTb, N. gonorrhoeae, Paracoccidioides brasiliensis, P. aeruginosa, S. aureus[2], salmonella,* SeV, *T. gondii*, TBEV, WNV	ATXN1, CTNNB1, IL12A, KRT2, MAML2, MECP2, NACA, NARS2, PDCD7, RIMS2, SPAG1, TCERG1, TNKS	34
34	BR-V-032	EBV[2], *H. pylori*, HBV, HCV, HEV3, HHV-8, HIV-1[2], HPV, HTLV-1, SV40	BUB1, ELP3, HNRNPU, LATS2, TAT, ZNF185	32
35	BR-V-033	ADV[3], *aspergillus fumigatus[2], aspergillus,* BKV [polyomavirus BK][2], *Borrelia burgdorferi, Borrelia spielmanii, C. difficile, candida albicans,* DENV[3], *E. coli,* EBV[8], *H. pylori*, Hantaan virus, HBV[3], HCMV[2], HCV[7], *H. influenzae*, HEV, HHV-8[2],HIV-1[8], HPV with HIV-1, HPV[5], HSV-1[4], HSV-2, HTLV-1[2], HTLV-1, IAV[3], *Leishmania infantium, Leishmania, L. monocytogenes, M. hyopneumoniae, MTb*, MCPyV, MMTV, oral bacterial infections, OROV, orthobunyaviruses, *P. falciparum, P. aeruginosa, Plasmodium chabaudi*, pneumococcal sepsis, RABV, RNA virus[3], RSV[3], RVFV[2], *S. aureus, S. pneumoniae, S. pyogenes, Salmonella,* septic shock, SeV[3], *T. gondii*, TBEV [tick borne encephalitis], WNV	BHLHE40, BRD4, CAND1, CD38, CFHR1, GHRHR, GLT6D1, HLA-A, HLA-G, KLKB1, MAVS, MBL2, MED13L, MPEG1, NFIC, OGT[2], PLCE1, PSD, SAT1, TGOLN2, TOM1L2, TP53, VTN[3]	80
36	BR-V-036	CVB3[MICE], Ebola, EBV[2], Gm positive bacteria, Gram negative bacteria, HBV[4], HCMV, HCV[5], HHV-8[2], HIV-1[6], HPV[4], HPV with HIV-1, HSV-1, HTLV-1, IAV[3], Legionella, MCPyV, Moloney murine leukemia virus, *P. aeruginosa, H. pylori*, respiratory tract infections, RVFV, septic shock, *T. cruzi*	ABL1, AOAH, BRCA1, BRD4, CALM2, CHD6, DST, F8, KALRN, LIMK1, MASP2, NRXN3, PLEC, TGM3, TP53, TPX2, TTN, ZFYVE20	70
37	BR-V-040	CMV[mice], Cryptons [DNA transposons], DENV, Ebolavirus, EBV[2], HBV [hot spot of recurrent integration of HBV genes], HHV-8, HIV-1[2], HSV[2], JEV, laryngotracheitis virus, *Listeria monocytogenes*, VSV, VZV	C8orf79, DIAPH2, MLL, RHOBTB2, TLR8, TUB1A1, ZMYM4	26
38	BR-V-045	*Aspergillus fumigatus, clostridium*, DENV, dsRNA virus, EBV, *H. pylori*, HBV[2], HCMV, HCV[2], HHV-8[2], HIV1, HPV with HIV-1, HSV-1, IAV, MCPyV, MV, *N. gonorrhoeae, plasmodium, pneumocystis carnii*, prion infection, RSV, RVFV, *Streptococcus B*	DST, ERBB2IP, PIGO, PRKRIR, RASA4, SLC12A3, TP53	20
39	BR-V-047	EBV[2], *E. coli*, enterovirus, *H. pylori*[2], HAV, HCMV, HDV, HHV-8, HIV-1, HPV, HTLV-1, *M. leprae, M.Tb.*, Mouse hepatitis virus, *Pasteurella pneumotropica, S. typhimurium (mice), T. gondii,* TMEV, *Vibrio parahaemolyticus*	COL13A1, DAPK1, LTA4H, NLRP4, SRF, ZNF148	17
40	BR-V-048	*Aspergillus fumigatus, clostridium*, DENV, EBV[2], HCMV, HIV-1[2], HPV[3], HSV-2, *N. gonorrhoeae*, RSV, *plasmodium*, prion infection, *Streptococcus B*, MHV68	CYP21A2, FOXO1, ITSN2, PRKRIR, DNAH3, GRIN2D, NCOR1, PIGM, PRDM5, MLXIPL, USP12	39
41	BR-V-051	BKV, *Campylobacter jejuni*, CMV, CVB3, *E. coli*, EBV[2], *H. pylori*[2], HBV[2], HCMV, HCV[2], HHV-8[2], HIV-1[2], HPV with HIV-1, HPV, HSV, JCV, *Leshmania major, MTb*, MCPyV, MMTV, *Rickettsiae*, RVFV, *S. aureus, S. typhimurium, T. cruzi, T. gondii*, VSV, VACV	KLRK1, TNFSF9, TP53, VCL, FGF23	15

Figure 2. Examples of steps in innate immune pathways altered by mutation in breast cancers. Breast cancers having mutations in a given gene are listed in red boxes with mutations being assumed as inhibitory. A few infections from the broad range of infections that interact with the pathways shown are arbitrarily selected to illustrate the potential for relationships among infections and gene mutation to exacerbate cancer. Orange boxes indicate inhibitory signals from infections, and light blue boxes indicate the gene is stimulated by the infection. In some cases, the protein product from the infection that affects the signal is given before the infection. Tables 2 and 3 give infections that are associated with damage to genes encoding many of the steps in the pathways shown.

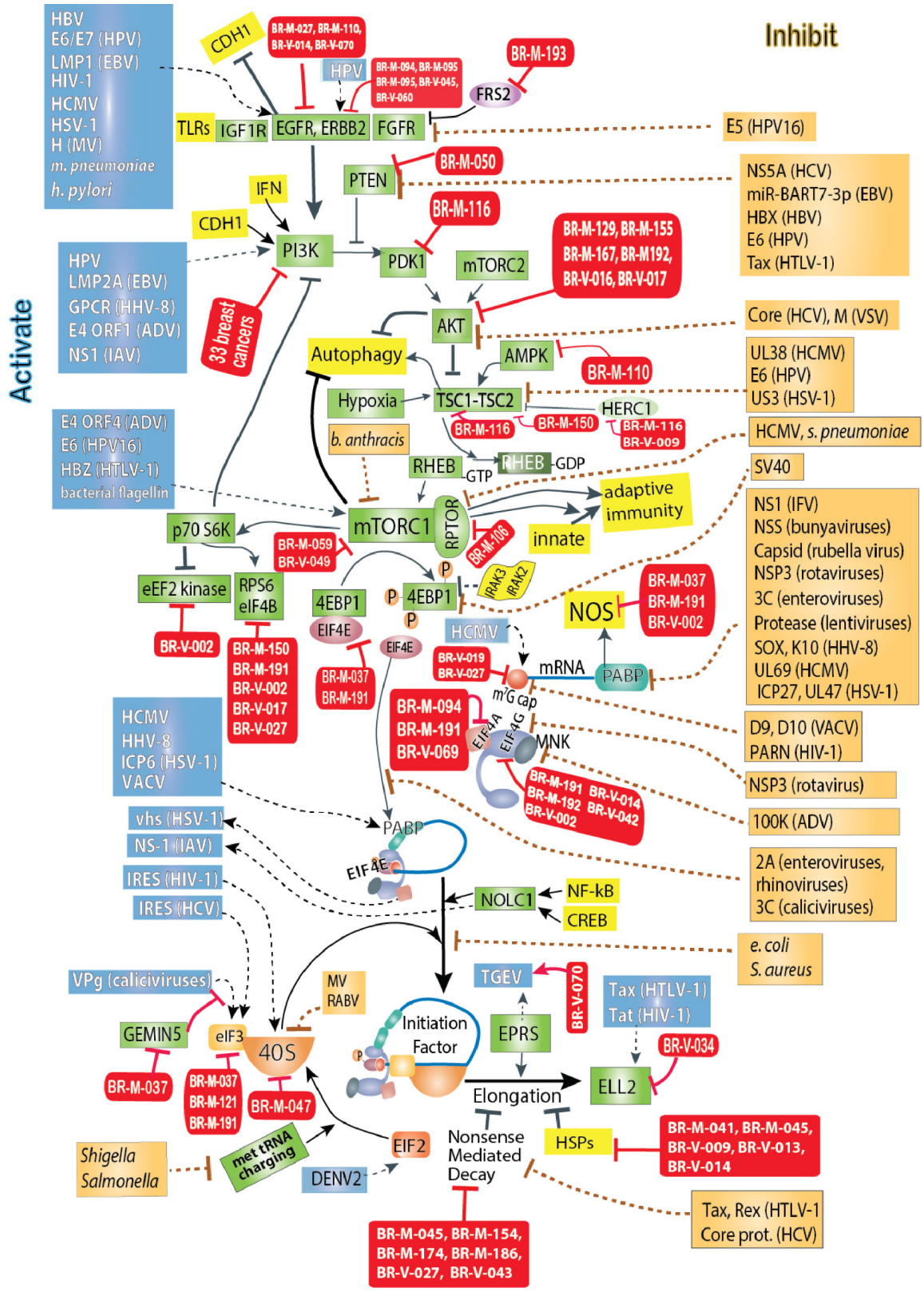

Figure 3. Mutations in breast cancers activate or inhibit human infections because they affect viral strategies for co-opting or inhibiting translation initiation. Breast cancer mutations occur at points in signaling pathways that control translation initiation and elongation and the same points are often targeted by multiple infections. The loss by the host of control of translation interferes with the host's ability to mount an innate immune response. Viruses and other infections target most steps in the translation process and coincide with mutations in multiple breast cancers. Infections that activate steps in the pathway are shown in blue boxes primarily at the left of the figure and infections that inhibit steps are shown in orange boxes primarily at the right of the figure. Yellow boxes indicate points of connection to immune response pathways. The diagram is adapted from the work of Walsh and Mohr. Breast cancer mutations may also affect translation elongation and NMD as indicated at the bottom of the figure.

inhibit rather than stimulate the affected gene. Infections, in contrast to mutations, may stimulate, inhibit, or commandeer gene function. The two figures began from the review by Walsh and Mohr[13] on the effects of viruses on protein translation. The figures show that many mutations converge with infections to deregulate many cellular pathways essential to defend against infection. The same probably holds true for metabolism and for other functions as well (data not shown).

There are many opportunities for breast cancer mutations and associated infections to exacerbate cancer risks. Only a few arbitrarily selected interactions are shown (Figs. 2 and 3) among components in these pathways versus infections, but they illustrate how known tumor viruses or other infections can evade immune responses and cooperate with, substitute for, or antagonize breast cancer mutations. Table 2 gives more detail of examples linking breast cancer mutations and specific infections or groups of infections.

Table 3 uses more traditional classification systems to separate infection-associated breast cancer mutations into diverse processes that they affect: innate and adaptive immunity, cell adhesion and tissue architecture, DNA damage response, protein transcription, mRNA splicing, RNA processing, protein translation, cell cycle control, metabolism, nucleocytoplasmic transport, and protein trafficking. Table 3 is intended to illustrate that the 1,077 different genes linked to infection can encode for widely different functions. There are only about 200 different genes used as examples in Table 3, but a current working list of all the mutations, the genes affected, and the associated infections is available as Supplementary Material. Beyond immunity and protein translation, most traditional cellular functions can be altered, deregulated, or subverted by infections. For example, normal cell morphology and metabolism in virally infected cells must be altered to convert the cells into viral factories. Changes in ionic strength or pH can sometimes affect infection such as by facilitating viral uncoating. These traditional functions are also targeted by mutation, although not necessarily at the same points (Figs. 2 and 3). An additional signaling pathway for metabolic generation of energy (not shown) further supports the biological plausibility of mutation and infection associations.

Examples showing mutation in diverse functions alter risks for infection.

Breast cancer mutations damage genes encoding for proteins in immune signaling pathways. Brief explanations for some of the steps shown in Figure 2 are given below. Multiple infections, even those not linked to cancer, can affect the response to tumor viruses and to mutations. For example, four breast cancers have mutations in a proteasome component, and many breast cancers have mutations that affect

Table 3. Individual breast cancer mutations deregulate the same cell signals as infections over a wide variety of processes.

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
Antiviral or immune response, autophagy, apoptosis			
AKT1	HCV,[60] Bacteria	BR-M-129, BR-M-155, BR-M-167, BR-M-192, BR-V-016, BR-V-017	Regulates defensin expression and the innate immune response important for bacterial clearance[61]
ADAR	DsRNA viruses[62]	BR-M-191	Viral defense. Adenosine to inosine in dsRNA substrates
BCL6	EBV[63]	BR-M-037	Regulation of innate immunity, macrophage morphology and motility
BMF	HHV-8[64]	BR-M-116	BCL2 homology domain 3 (BH3) binds BCL2 proteins to regulate apoptosis. Dynein L-chain binding associates it with myosin V. Protein limits HHV-8 (KHSV) replication[64]
BPI, BPIL1	Gram negative bacteria, *MDR pseudomonas, MDR acinetobacter, E. coli*[65]	BR-V-002, BR-M-041	Neutralizes endotoxins and carries outer membrane antigens from gram negative bacteria to dendritic cells[66]
BRAP	EBV[67]	BR-M-094	Negative regulator of import of viral proteins[68]
BLZF1	EBV,[69] DENV	BR-M-045	Methylation of cytosine, may interact with-TRAFF1,[70] NFKB-p65 in innate immune pathways
CASP2	*Francisella tularensis*,[71] *S. aureus, Aeromonas,* MMTV (mice)	BR-M-047, BR-M-189	Autophagy control, cell death pathways, death due to cytoskeletal disruption[72]
CBLB	LCMV,[73] MV, *Mycobacterium leprae*,[74] *P. aeruginosa, E. coli sepsis, Burkholderia cenocepacia*	BR-M-110	E3 Ubiquitin ligase. Controls spontaneous antitumor activity of cytotoxic T cells in different cancer models[75]
CCL1	*Listeria monocytogenes*,[76] *Borrelia burgdorferi*, A/H1N1 virus, *MTb*, VSV, *S. aureus,* herpesvirus saimiri	BR-V-027	Regulates immunity, inflammation.[76] Secreted by activated T-cells[77]

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
CCR2	IAV,[78] *S. aureus*, CVB3, HIV-1, HCMV, CHIKV, HHV-6B, WNV, MV, TMEV, *Toxoplasma gondii, Listeria monocytogenes, C. albicans*	BR-M-191	Monocyte chemokine receptor[79]
CD1a/R4/T6/CD1/FCB6/HTA1	HCV, HIV-1, HTLV-1,[80] *Borrelia burgdorferi,* polyoma virus, mycobacteria,[81] TGEV	BR-M-110, BR-M-174	Related to major histocompatibility proteins. Mediate antigen presentation of a broad range of lipid based antigens to T cells[82]
CD320/8D6/8D6A/TCBLR	EBV,[83] HIV-1	BR-V-011	B-cell multiplication and immunoglobulin secretion,[84] Transcobalamin receptor
CD38	EBV,[85] *Listeria monocytogenes*, HIV-1	BR-V-033	Enzyme expressed in leukocytes, functions in cell adhesion, signaling, calcium signaling
CD3D	Severe bacterial, viral or fungal infections inactivation causes SCID, post-op sepsis,[86] EBV	BR-V-043 (synonymous)	T cell receptor complex
CD59	HHV-8, DENV,[87] *E. coli,* HBV, *Borrelia, Gardnerella vaginalis,* HHV-7, HSV-1	BR-V-054	Complement regulatory protein
CEBPZ	*Cryptococcus neoformans,* HIV-1, MTb[88]	BR-M-193	Regulates gamma IFN response, antimicrobial peptide production[88]
CFHR1, CHFR4	*P. aeruginosa, S. pneumoniae, S. pyogenes, entero-hemorrhagic E. coli, Borrelia burgdorferi, C. albicans,*[89] *A. fumigatus, Borrelia spielmanii, H. influenzae, Yersinia pseudo tuberculosis*	BR-V-033 (synonymous) BR-M-169(synonymous)	Complement regulation
CSF3R/CD114/GCSFR	*MTb., C. trachomatis,* DENV, HCMV,[90] IAV, HIV-1, Rubella virus, *L. monocytogenes, Pseudomonas aeruginosa*	BR-M-123	Receptor for colony stimulating factor 3, a cytokine that controls granulocytes
CTSD	HBV, *H. pylori*[91]	BR-V-044	Lysosome function
GAS6	Enveloped viruses including VACV, DENV, WNV, Ebola[92]	BR-M-158	Phagocytosis of dead cells[93]
CIITA	Herpes viruses,[94] *T. gondii*, HBV, mycobacteria, HHV-8, lymphocytic choriomeningitis virus (LCMV), influenza virus, HIV-1, *Cryptosporidium parvum*, HCV, HBV, HHV-6, HPIV3, HTLV-2, CMV, EBV, *chlamydia*,	BR-V-009	Master control transactivator for expression of class II major histocompatibility genes
HLA-A, B, C, G,	DENV, *MTb*, IAV, tick borne encephalitis (TBEV), HIV-1, HBV, ADV, HSV-1, HSV-2, EBV, HTLV-1, polyomavirus BK (BKV), rift valley fever virus (RVFV), HPV, Hantaan virus. HLA-G: HBV, HCV, *T. gondii,* septic shock, *P. falciparum*, *Leishmania infantium*, HIV, HSV-1, RABV, IAV, HPV, HCMV	BR-M-037, BR-M-150, BR-V-033, BR-B-042, BR-V-043	Antigen presentation of intracellular degradation products from proteasome
GZMA, GZMH, PRF1	Bacterial sepsis, *m. leprae*, Marek's disease virus, *L. donovani*, HIV-1, rabies virus, severe sepsis, H1N1 virus, helminth, RSV infection, LCMV, poxvirus (mice), *P. falciparum*, gram negative bacteria, herpes, CMV, EBV, HTLV-1, HBV, ADV, DENV, VACV, *Y. pseudotuberculosis*, orthopoxvirus	BR-M-047, BR-V-027, BR-V-050	NK and CTL effectors that can be expressed by other immune cells as well. Cytotoxic granules delivered to virus infected and transformed cells
HUWE1	HIV-1[95]	BR-M-116, BR-M-172, BR-M-191, BR-M-192	Interactor of HIV-1 Gag-Pol through integrase
IRAK2, IRAK4, IRAK3	ADV, CMV, EBV, HSV, MHV-8, VZV, and VACV	IRAK2: BR-M-037; IRAK3: BR-M-191; IRAK4: BR-M-045	Signaling from innate immune receptors
JAK, JAK-STAT pathway	*L. donovani*, *MTb*, HCV, HHV-8, IAV, DENV, EBV, CMV, JEV, RSV,[96] MV, MMTV, TGEV, VSV	BR-V-021, BR-V-043, BR-M-172	IFN cytokine production
LAMP2	HCV,[97] CVB3, VACV, *Neisseria*	BR-M-154	Chaperone-mediated autophagy and RNA- and DNA-targeting autophagy[98]
LGR4	Septic shock[99]	BR-M-166	Negative regulator of pattern recognition and some innate immune responses[99]

(*continued*)

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
MAVS	DENV,[100] ADV, EBV, HCV, HSV	BR-V-023, BR-V-033	Sensing of viral RNA via RIG-1 receptor Triggers IFN response
ND10 complex (Sp100, Daxx, PML, ATRX)	HSV-1 (degrades PML and Daxx), VZV (degrades PML) and HCMV (degrades SP100), HPV	BR-M-172, BR-M-120, BR-V-002	Intrinsic immunity to viruses
NLRP3	CVB3, DENV, EBV,[101] IAV, HCV, HSV-1, HTLV-1, HIV-1, RSV	BR-M-158, BR-M-191, BR-V-070	Cytoplasmic sensor of infection. The OAS-RNase L system is a major mechanism of activation
NMD: SMG1, SMG5, SMG7, UPF2[102]	HTLV-1, HCV, positive strand RNA viruses, SFV	BR-M-045, BR-M-154, BR-M-174, BR-M-196, BR-V-027, BR-V-043	Intrinsic immunity to remove abnormal mRNAs with premature termination codons
PIKFYVE	HIV-1, *plasmodium, salmonella*	BR-M-045	Innate immune signaling against virus.[103] Facilitates IFN production to inhibit HIV-1 for example
PRKCB	HCV, RSV, MMTV[104]	BR-V-067	Apoptosis, antibody production, cell proliferation[105]
PPP1R15A	HTLV-1, HCV, CHIKV, CVB3, DENV, VSV, HSV-1	BR-M-041	Regulates cytokine production[106]
PRKRIR	NDV, VSV	BR-M-191, BR-V-045, BR-V-048, and BR-V-069	PRKRIR increases type I IFN production by preventing degradation of the RIG-1 receptor to inhibit viral replication[107]
PSMD2, PSMC6, PSME3	EBV, *S. aureus* (mice)	BR-M-085, BR-M-094, BR-M-034, BR-M-037	Non-catalytic subunit of proteasome activated by TNFα. Processing of MHC peptides for presentation to adaptive immune system [Gene database]
RIOK3	Murine gammaherpes virus, IAV	BR-M-116, BR-V067	Adapter protein bridging TBK1 and IRF3 to mediate antiviral IFN production[108]
TAP2, TAPBP, TAPBPL?	DEENV, EBV, HBV, HCMV, HCV, HIV-1, HPV, Marek's disease virus, Hantaan virus (HTNV), HIV-1	BR-M-045, BR-M-110	HLA antigen presentation[109]
TAS1R1, TAS1R2, TAS1R3, TAS2R5	LPS endotoxin from Gram negative bacteria	BR-M-076, BR-M-154. BR-V-009, BR-V-014, BR-V-037, BR-V-038, BR-V-060	Markers for circulating leukocytes subpopulations.[110] Neurological system that detects bacterial pathogens. LPS initiates TLR4 signals that downregulate receptors
TFG	VSV[111]	BR-M-191, BR-V-009	Regulates IFN-β production[112]
TLR3	HSV, herpes simplex encephalitis, JEV, CMV, ebolavirus VP35, EBV, DENV	BR-V-067, BR-M-037	Innate immunity receptor
TLR8	ssRNA viruses such as HCV originally, but also HPV16, EBV	BR-V-040	Innate immunity endosomal receptor, clearance of HPV, inhibited by EBV
TRIM4	SeV, VSV	BR-M-122, BR-V-003	Immune specific adapters, involved in viral infection
ULK1	HIV-1, HIV-2, *Brucella abortus*	BR-V-027	Regulates autophagy[113]
Cell structural barriers, nucleosomes, chromatin, adhesion, cell morphology, volume, development			
ARAP2	Resistance to *L. monocytogenes*	BR-M-193	Essential signaling protein for cytoskeletal remodeling and internalization of Listeria.[114]
B3GAT3	Mutation increases resistance to *Chlamydia trachomatis*	BR-V-014	B3GAT3, B4GALT7, and SLC35B2, which encode sugar transferases and the 3′-phosphoadenosine 5′-phosphosulfate transporter 1, facilitate Chlamydia infection[115]
CALD1	HHV-8	BR-M-094	Microfilament organization, thus cell shape, adhesion, and invasion. Links HHV-8 infection to actin cytoskeleton[116]
CCT2	rabies (RABV), *B. anthracis*, influenza, EBV(+)	BR-V-060	Chaperonin, folds actin and tubulin[117]
CD93	Parvovirus B19, Gm negative bacteria	BR-M-041	Intercellular adhesion, apoptotic cell clearance
CEACAM8	Bacterial infections[118]	BR-M-005	Response to bacterial DNA

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
CDH1, CDH2	Coxsackie, ADV, *H. pylori*, HPV, HBV, HCV, Junin virus, RSV, *bacteroides fragilis, clostridium botulinum*, EBV, *Neisseria gonorrhoeae* CDH2: HHV-8	BR-M-126, BR-M-166, BR-V-022. CDH2: BR-M-041, BR-M-129	Cell-cell contact, Connections to adaptive immunity
CHD3,[119] CHD6, CHD8	CHD3: HSV CHD6: Influenza, HPV; CHD8: *Fusobacterium*	CHD3: BR-M-080, BR-V-067. CHD6: BR-M-080, BR-V-036, BR-V-064, CHD8: BR-M-200	Nucleosome, chromatin remodeler, helicase DNA binding proteins
CLDN6, CLDN14	*H. pylori*, *clostridium perfringens*, RSV, *Campylobacter jejuni*, HCV[120]	BR-M-120, BR-M-116	Participate in forming epithelial tight junctions among cells, to regulate solute and ion movements. HCV entry factors
CTTN	*E. coli*, *Shigella, Neisseria, Rickettsia, Chlamydia, Staphylococcus and Cryptosporidium, Listeria, Shigella,* Myxoma virus, VACV, *H. pylori*	BR-M-167	Actin cytoskeleton regulator.[121] All viruses must pass through barriers such as cortical actin[122]
COL13	Mouse hepatitis virus, the TMEV, *H. pylori, Pasteurella pneumotropica*	BR-V-043, BR-V-047	Transmembrane collagen, involved in cell-cell and cell-matrix contacts
DAAM1	*Borrelia burgdorferi*[123]	BR-V-016, BR-V-022	Formin family member. Filopodia formation cytoskeletal remodeling[124]
DIAPH1	VACV	BR-M-037	Regulation of microtubule polymerization and actin barriers[125]
DLG1	HPV, HTLV-1, IAV, HIV-1	BR-M-106	Normal development, scaffolding, cell-cell contacts[126]
FLG	Viral, bacterial, and fungal infections	BR-M-045, BR-M-169, BR-M-191, BR-M-193, BR-V-028, BR-V-030, BR-V-044, and BR-V-060	Intermediate filaments marker for epidermal differentiation[127]
HDAC1, 5, 9, HDGFRP2, HERC2	HIV-1,[128] HTLV-1, IAV, mouse gamma herpesvirus68, Marek's disease virus (poultry)	BR-M-037, BR-M-154, BR-M-055, BR-M-165, BR-V-019, HERC2: BR-M-026, BR-M-080	Chromatin structure accessibility, HDAC5 forms complex that controls inflammation, HDGFRP2 controls HIV site integration under some conditions. HERC2 ubiquitylates Histone H2A
Histones, histone components	HHV-8, HIV-1, HSV1, [HIST1H1A in BR-M-027] retroviruses Histone 1H3B [mutated in BR-M-041, BR-V-016, and BR-V-047] is associated with sepsis lethality in rodents. HMG20A a histone component is associated with VACV in BR-M-030	BR-M-027, BR-M-030, BR-M-037, BR-M-041, BR-M-045, BR-M-047, BR-M-055, BR-M-076, BR-M-098, BR-M-121, BR-M-166, BR-M-189, BR-V-016, BR-V-026, BR-V-027, BR-V-034, BR-V-044, BR-V-049, BR-V-054	Histone H1 regulates silencing of IFN regulated transcription and its chaperone TAF-1.[129] Other histones participate in DNA structures that affect retroviral integration sites. Chromatin structure is important in determining mutation rate
JARID2	HCMV,[130] Reticuloendotheliosis virus strain T	BR-M-191, BR-M-193	Jarid2 methylation fine-tunes methylation of H3K27 to affect chromatin structure[131]
HS3ST3A1	HIV-1 maternal fetal transmission, *P. falciparum*, HPV?	BR-V-014	Heparan sulfate biosynthesis
KDM4A	HHV-8[36]	BR-M-045, BR-M-191, BR-V-017	Nuclear protein is a trimethylation specific demethylase converting specific histone trimethyl lysines to dimethyl lysine residues. Transition of embryonic cells to endothelial cells[132]
ITGAX	IAV, HCMV, HCV, WNV, BLV, ADV, HIV-1, HBE, HBV, JEV, MRSA, HSV-1, DENV	BR-V-023	Integrin complement component receptor. Cell adhesion complexes, immune trafficking, cross presentation of antigens to T-cells
Keratins	HPV, ADV, HCV progression and liver fibrosis	BR-M-027, BR-M-028, BR-M-036, BR-M-037, BR-M-038, BR-M-094, BR-M-123, BR-M-165, BR-M-198, BR-V-002, BR-V-007, BR-V-031, BR-V-037, BR-V-039, BR-V-043	Cytoskeletal structure, epidermal barrier

(*continued*)

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
LGALS9	DENV,[133] HBV, HCMV, HCV, HIV-1, Influenza, *MTb, pneumococcus*	BR-M-073, BR-M-191	Codes for a beta-galactoside binding protein that regulates interactions among cells and between cells and the extracellular matrix.[134] Stabilizes regulatory T-cells[135]
MAPRE2	HCMV[136]	BR-M-047	Codes for a protein associated with microtubules needed for spindle structure in mitosis. Homologous to APC gene associated with hereditary colon cancer
MLL genes	EBV, HBV, HHV-8, HIV, VZV	BR-M-027, BR-M-055, BR-M-076, BR-M-116, BR-M-126, BR-M-186, BR-M-193, BR-V-011, BR-V-013, BR-V-016, BR-V-021, BR-V-027, BR-V-040, BR-V-064	Histone methyl transferases[137] that are common sites of viral integration
MUC2	*Clostridium perfringens, Campylobacter jejuni, C. difficile, Clonorchis sinensis*, EBV, *E. coli, Entamoeba histolytica*, HBV, HCMV, HCV, HHV-8, hMPV, HPV[4], *H. pylori*, HIV-1, HSV-1, IAV, *L. monocytogenes, P. aeruginosa*, RSV, RV14, sepsis, *S. typhimurium, Shigella, T. spiralis*	BR-M-005, BR-M-030, BR-M-047, BR-M-080, BR-M-005, BR-M-083, BR-M-098, BR-M-120, BR-M-167, BR-M-169, BR-M-085	Mucin, lubrication, protective barrier
MYC	BKV, HCV, EBV,[138] HPV, *H. pylori*, MDV, HIV-1, *M. bovis* (cattle), HHV-8, HBV, FV, *T. gondii,* avian leukosis virus (chickens), TTVs	BR-M-189	Regulates global chromatin structure by affecting histone acetylation in regions close to and far away from genes. Also affects cell cycle progression and apoptosis. Rearranges associated with EBV infection causes Burkitt's lymphoma
NCOR	EBV,[139] HIV-1, HTLV-1	BR-M-166	Chromatin structure modification to control levels of transcription
NEDD4L	EV71,[140] HIV-1	BR-V-014	Regulates cell surface expression of sodium channel, cell volume and membrane proteins, facilitates virion release
RANBP2	HIV-1, JEV	BR-M-150, BR-V-009	Nucleoporin, nuclear import positively selected by HIV-1 infection[141]
SDC1	EBV, HCV, HHV-8, HIV-1, HPV,[142] HSV-1, *S. aureus, P. aeruginosa, plasmodium falciparum*	BR-M-150, BR-V-067	Cell binding, cell shape, host cell viral receptors
SMARCA2/BRM, SMARCA4	HIV-1, HPV, HTLV-1[143]	BR-M-074, BR-M-193, BR-V-009, BR-V-019	Chromatin structure based gene regulation. Component of SWI/SWF remodeling complex required to activate chromatin repressed genes
SSRP1	HHV-8, MCMV, *T. gondii*[144]	BR-M-095, BR-M-166	Chromatin and nucleosome management
TTN	HPV16[4], HCV, CVB3 (mice)	BR-M-005, BR-M-026, BR-M-037, BR-M-050, BR-M-076, BR-M-079, BR-M-166, BR-M-174, BR-V-008, BR-V-019, BR-V-022, BR-V-034, BR-V-036, BR-V-042, BR-V-050, BR-V-067	Crosslinks proteins in the cytoskeleton and provides elasticity. TTN associates with chromatin in the nucleus where its functions are probably similar to those in the cytoplasm
VCL (vinculin)	*Campylobacter jejuni, Enterohemorrhagic E. coli,* CVB3, *S. aureus, H. pylori*,[145] HIV-1, *T. Cruzi*, *rickettsiae*, VaCV, *Listeria monocytogenes, Shigella flexneri*	BR-V-051	Cytoskeletal protein F-actin anchor, involved in cell junctions with other cells and with ECM
WDR1/AIP1	SeV[146]	BR-M-174	Cell shape dynamics. Binds to SeV M protein
Cell cycle, cell growth			
ANAPC1	ADV, EBV,[147] HBV, HCMV, HPV, HTLV-1	BR-M-030, BR-V-070	Regulates progression through the cell cycle
BRAF	Vesicular stomatitis virus infection in melanoma[148]	BR-M-116	Signal transmission to direct cell growth. The RAS–RAF–MEK–ERK–MAP kinase pathway mediates the cellular response to growth signals

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
CDC27	CHIKV[149]	BR-M-047	Timing of mitosis
CGRRF1	EBV[150]	BR-M-026	Cell growth regulator
CRY1, CRY2	HCV[151]	BR-M-174 (CRY1), BR-V-037 (CRY2)	Regulates circadian clock
EGFR	AAV, ASFV, EV71, HBV, HCV,[152] HCMV, HSV, EBV, IAV,[152] HPV, RSV, HPIV, PICV, VACV, CPXV, SFV, HIV, AEV, *mycoplasma, C. trachomatis*	BR-M-027, BR-M-110, BR-V-014, BR-V-070	Receptor tyrosine kinase, cell cycle, cell cytoskeleton
GHR	HCV[153]	BR-M-110	Cytokine that is transmembrane receptor for growth hormone. Inversely related to expression of IL-1β, IL-18, TNF-α) and acute-phase proteins (SAA, Hp)
GRP	Sepsis, *H. pylori*[154]	BR-V-043	Gastrin releasing peptide. Promotes epithelial cell multiplication
PIK3CA	HBV, HCV, HPV,[155] MCPyV	BR-V-003, BR-M-050, BR-M-083, BR-M-098, BR-M-184, BR-V-015, BR-V-020, BR-V-021, BR-V-024, BR-V-027, BR-V-034, BR-V-052, BR-V-064, BR-V-071, BR-M-026, BR-M-028, BR-M-030, BR-M-036, BR-M-055, BR-M-059, BR-M-083, BR-M-116, BR-M-120, BR-M-121, BR-M-150, BR-M-158, BR-M-165, BR-M-166, BR-M-169	Regulator of cell growth and apoptosis
PP2A	MCPyV[156], SV40	BR-M-037, BR-M-116, BR-V-002, BR-V-008	One of 4 central Ser/Thr phosphatases. Negative control point for growth and cell division
PKMYT1	HHV-8[157]	BR-M-191	Negative regulator of G2/M transition in cell cycle
RPRM	EBV,[158] *H. pylori*	BR-V-024	Cell cycle arrest at G2M upregulated by LMP-1 in EBV infection
URGCP	HBV (X protein)[159]	BR-M-189	Upregulator of cell proliferation
WEE1	HHV-6[44]	BR-M-191, BR-V-027, BR-V-030	WEE1 coordinates the transition from DNA replication to mitosis. WEE1 is elevated on HHV-6 infection of immune cells and works to stop cell division.
DNA repair, DNA damage response			
APEX1, APEX2	HPV, HIV-1[160] APEX3: HCMV, *H. pylori*	BR-V-002, APEX2 (BR-M-037)	Major human apurine/apyrimidine endonuclease. APEX2: Base excision repair of apurine/apyrmidine lesions
BRCA1	High risk HPV, EBV, *H. pylori*, HIV-1, HBV or HCV	BR-V-036 BR-M-027	Repair of complex DNA damage, double strand break repair
BRCA2	High risk HPV,[161,162] EBV[163]	BR-V-023 BR-V-037	Repair of complex DNA damage, double strand break repair
BUB1, BUB3	HHV-8, SV40, HPV, HTLV-1, EBV, HCMV (BUB3)	BUB3: BR-M-116, BR-V-014, BUB1: BR-V-032	Spindle assembly checkpoint, DNA damage response
FANCC, FANCF, FANCI	SV40, HPV,[164] EBV, *pneumococcus*, viral hepatitis	BR-M-116, BR-M-122, BR-M-158	Repair of complex DNA damage, genomic stability
H2Ax/H2AFX	EBV,[165] HHV-8, HTLV-1, BKPyV, HPV, HCMV, ADV, HBV, VZV	BR-M-116, BR-V-064	Double strand break repair (early indicator), homologous recombination, NHEJ
MDC1	EBV,[166] *H. pylori*, HTLV-1	BR-V-002	Checkpoint activation in response to DNA damage

(*continued*)

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
PNKP	HSV-1	BR-M-094	DNA repair of radiation or oxidative damage
TP53	MCPyV, HPV with HIV-1, HBV, EBV, *H. pylori*, HCV, HCMV, RVFV, HHV-8	BR-V-002, BR-V-007, BR-V-008, BR-V-012, BR-V-014, BR-V-022, BR-V-024, BR-V-027, BR-V-033, BR-V-036, BR-V-037, BR-V-043, BR-V-045, BR-V-050, BR-V-051, BR-V-060, BR-V-067, BR-V-071, BR-M-005, BR-M-034, BR-M-045, BR-M-073, BR-M-085, BR-M-094, BR-M-095, BR-M-122, BR-M-189, BR-M-192, BR-M-123, BR-M-166	Response to DNA damage to induce cell cycle arrest, apoptosis, genomic stability, modulates immune responses
XPC	MCPyV,[167] *H. pylori*	BR-M-037	Nucleotide excision repair
Transcription, mRNA, processing, splicing			
BRD4	HPV-16, HHV-8,[168] HIV-1, EBV	BR-V-033 BR-V-036	Brd4 protein is essential in damage response to form nuclear foci. Latent episomal HHV-8 genomes form nuclear micro-domains, containing BRD2 and BRD4 chromatin modulators.[168] Competes with HIV-1 Tat for transcription activation
CSTF2T	HCMV, enterovirus	BR-V-050	Host cell mRNA polyadenylation
DDX-4, 11, 20, 21, 46, 47, 50, 51 and 53	IAV, reovirus, DsRNA viruses, HPV, EBV, HIV-1[169]	BR-M-028, BR-M-037, BR-M-055, BR-M-105, BR-M-154, BR-V-007, BR-V-034, BR-V-067	Unwinds dsRNA
DGCR8	HBV,[170] Enterovirus 71 (EV71), HTLV-1, IAV, HHV-8	BR-M-079	Subunit of the complex mediating release of microRNAs from the primary microRNA transcript. This protein is required in the complex for binding the dsRNA and enhances its ability to cleave the RNA
INTS6	EBV[171]	BR-V-024	Integrator complex subunit 6/DICE1. Putative RNA helicase. Interacts with RNA pol II End processing of snRNA's
MED12, MED 13, MED12L, MED13L, MED14, MED23, MED25, MED28	Bacterial infection (drosophila),[172] HIV-1	BR-M-059, BR-M-150, BR-M-165	Initiation of transcription mediator complex subunits. Complex is required for defense of bacterial infection in drosophila. The mediator complex links gene-specific transcriptional activators with the basal transcription machinery
SFRS1	HIV-1[173]	BR-M-154	An SFRS1 interacting protein is the cellular binding partner of retroviral integrase proteins Knockdown of SFRS1 can alter expression of different p53 forms
SRRM2	HTLV-1,[174] HIV-1	BR-M-055, BR-M-193, BR-V-002, BR-V-067	mRNA alternative splice site selection
TAF1	HSV-1, HPV[175]	BR-M-073, BR-M-098	RNA polymerase function
Translation, ubiquitylation, proteolysis			
CAND1	EBV[176]	BR-V-033	Ubiquitin ligase regulator. Protein degradation. Controls interactions between many proteins and binding platforms
EIF2 isoforms	HCV,[177] *E. coli (Shiga-toxogenic)*	BR-M-155, BR-V-002, BR-V-031, BR-V-033	Translation initiation factor
FTSJD1	IFV, bunya viruses, rubella, rotavirus, enterovirus, lint virus, HHV-8, HCMV, HSV-1, VACV all inhibit m7G cap	BR-V-027	2-O ribose methylation of the m7G cap of mRNA[178]

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
NARS2, NARS4	*S. aureus, H. pylori*	BR-V-024, BR-V-031	Asparaginyl-tRNA synthetase
RNGTT	HERV[179]	BR-M-055	Enzyme required for 7 methyl-guanosine mRNA cap formation. Intron contains HERV provirus
RPS3	HCV, *P. aeruginosa*	BR-V-043	Ribosomal protein with functions beyond translation. Involved in innate immunity, apoptosis, and DNA repair
RPTOR	HCMV[41]	BR-M-106	Regulator of mTOR complex 1. Negatively regulates mTOR kinase. MTORC1 couples immune and metabolic programming, Regulatory T-cell function, NK cell differentiation. HCMV alters specificity
UBR4	HPV16,[180] DENV	BR-M-005, BR-M-169	Ubiquitin ligase component, interacts with nuclear RB4 and cytoplasmic calmodulin. Targeted by HPV16 and co-opted by DENV
ZC3H7B/RoXaN	Rotavirus[181]	BR-M-192, BR-V-042	Translation regulation. Cytoplasmic polyA binding protein forms complex with EIF4G and rotavirus
Homeostasis			
APNLR	HIV-1[182,183]	BR-M-110	Regulates the cardiovascular system, central nervous system and glucose
CALCR	Potentially critical for HSV infection[184]	BR-V-060	Calcium homeostasis (essential for immune responses)
CBFB	HIV-1,[185] polyoma, HPV	BR-V-051, BR-M-167, BR-V-021, BR-M-155, BR-M-172	Master regulator of blood cell formation
C1GALT1C1	*H. pylori*[186]	BR-V-044	Molecular chaperone required for full activity of the core galactosyltransferase Biosynthesis of di-, oligo- and polysaccharides.
CAPRIN1, CAPRIN2	JEV, EBV[187]	BR-M-095, BR-V-013	Stress granule formation (CAPRIN1), Wnt signaling enhancer (CAPRIN2)
CREB3L1, ATF6, CRTC2, CRTC3, CREB5[188]	WNV, HCV, Sendai virus, mouse gamma herpesvirus, HPV, HIV, HSV, HCMV, HTLV-1, EBV, *toxoplasma gondii* (BR-V-13, BR-M-027) XMRV retrovirus (CREB5)	BR-M-027, BR-M-155, BR-V-013, BR-V-039, BR-V-028, CREB5: BR-M-193	Intra-membrane stress response CREB5 a proviral insertion site for XMRV retrovirus
Trafficking, transport			
Dynein genes (DHAH, DNAL, DYN)	ADV, DENV, HIV-1, HPV,[189] rabies(RABV), reovirus, *Salmonella Typhimurium, Chlamydia psittaci, Aspergillus nidulans, Trypanosoma cruzi*	BR-M-027, BR-M-028, BR-M-038, BR-M-038, BR-M-074, BR-M-105, BR-M-106, BR-M-150, BR-M-191, BR-V-014, BR-V-022, BR-V-026, BR-V-027, BR-V-043, BR-V-048, BR-V-054, BR-V-070	Molecular motors for transport along microtubules[23] Essential for function of TRIM5α, a retroviral restriction factor that interferes with uncoating and reverse transcription. Essential for cilia function
HSP90B1, HSP90AA1, HSPA8, HSPBP1, HSPH1	CHIKV, HIV-1, HPV,[190] HBV,[191] HSV-2, VZV, Polyoma virus, CoxsackieB3 (CVB3), rotavirus, HTLV-1, SV40, EBV, prion disease	BR-M-041, BR-M-045, BR-M-154, BR-M-198, BR-V-009, BR-V-013, BR-V-014	Chaperone for folding TLR receptors, integrins, and other proteins to control exit from, ER
KALRN	HIV-1[192]	BR-M-120, BR-V-036, BR-V-043	Interacts with the huntingtin-associated protein 1, which is apparently involved in vesicle trafficking[192]
KIF-1A	HIV-1, HSV-2[193]	BR-M-028, BR-M-073	Molecular motor, intracellular trafficking
LYST	*S. aureus, candida,* EBV,[194] multiple infections	BR-M-037	Lysosomal trafficking regulator, deficit causes immunodeficiency disease Chediak-Higashi syndrome
NMT1	HIV-1[195]	BR-M-041	Modification of proteins to target them to membranes

(*continued*)

Table 3. (*Continued*)

MUTATED GENE IN BREAST CANCER	ALTERED SUSCEPTIBILITY TO VIRUS OR OTHER INFECTIONS PREDICTED DUE TO MUTATION OR DYSREGULATION OF GENE	BREAST CANCER(S) CONTAINING THE MUTATED GENE	NORMAL FUNCTION OF PROTEIN ENCODED BY MUTATED GENE OR IN INFECTION
PACS1	HIV-1,[196] HPV, MLV (murine leukemia), RD114, HCMV	BR-V-002	Regulated sorting of proteins in trans Golgi network to proper compartment, an important component of their in vivo activity Crucial for assembly of some retroviruses and essential interactions with some herpesviruses envelopes
RAB7A	HBV,[197] HIV-1	BR-M-186	Molecular switches, trafficking
SLC6A3	HIV-1[198]	BR-V-003	Dopamine transporter
STARD3	Subverted by a bacterial infection *Anaplasma phagocytophilum* for a bacterial inclusion membrane[199]	BR-M-121	Cholesterol export
STAU1	HCV,[200] HIV-1, HERV-K, IAV	BR-V-015	mRNA transport to different organelles
TF (transferrin)	HIV, HCV, HBV,[201] *Neisseria meningitidis, Burkholderia cenocepacia, Enteropathogenic E. coli, streptococcus, MTb*, canine parvovirus, *plasmodium*	BR-M-037	Within their host, pathogenic bacteria acquire iron essential for infection and growth from TF, a crucial innate immune defense protein
Metabolism			
ADPRHL2	Bacteria[202]	BR-V-020	Removes bacterial ADP ribosylation added by toxins from host proteins
AOAH	Gram negative bacteria[203]	BR-V-036	Acyloxyacyl hydrolase hydrolyzes fatty acyl chains from bacterial lipopolysaccharides, to detoxify them. The AOAH protein may modify host inflammatory responses to gram-negative bacteria
CA4	Renal bacteria, many CO2 sensing bacteria[204]	BR-M-079	Reversible hydration of carbon dioxide
CPT1A	Lower respiratory tract infection, *hemophilus influenzae, pneumococcus, C. trachomatis*,[205] HCV	BR-V-043	Long chain fatty acid metabolism, transport into mitochondria
CYP2C8	HPV[206]	BR-M-105	Steroid hydroxylation e.g. estradiol
FASN	DENV, HCV, HHV-8,[207] Rotavirus, HIV-1	BR-V-023, BR-V-052	Long chain fatty acid synthesis
G6PD	HPV, HBV,[208] HBE, DENV, HIV-1, *P. falciparum, P. vivax*	BR-M-122	Needed for pentose phosphate pathway to supply reducing energy as NADPH to cells
GRB14	*N. gonorrhoeae*, pathogenic bacteria[209]	BR-V-012, BR-V-070	Interacts with insulin and insulin-like growth factor receptors. Regulates response to infection with pathogenic bacteria
LCT/lactase	Rotavirus,[210] *Giardia lamblia*, HIV-1	BR-M-191	Lactose metabolism
LDLRAP1	*E. coli* uropathogenic[211]	BR-M-045	LDL receptor adaptor. Used as an alternate receptor by *e. coli*[211]
MGAM	DENV,[212] EBOLA, HCV, Marburg virus, MV, VZV	BR-M-037, BR-M-106, BR-V-034	Alpha glucosidase, starch digestion. Inhibition of this enzyme can impair the assembly of viral structural proteins and viral particles
NR1D1	*MTb*, *salmonella*, bacteria[47]	BR-M-079	Circadian clock
PAH	HCV impairs activity, HIV-1,[213] *P. falciparum*, viral encephalitis, yellow fever, bacterial infections	BR-M-191	Hydroxylation of phenylalanine converting it to tyrosine
PC	HCMV inhibits, HSV-1 induces[214]	BR-M-191	Pyruvate carboxylase converts pyruvate to oxaloacetate
PDXK	HIV-1,[215] HBV, Rauscher Leukemia virus, oncornaviral DNA polymerases	BR-V-016	Phosphorylates vitamin B6, required to convert B6 to pyridoxal phosphate
UPRT	EBV[216]	BR-M-174	Pyrimidine salvage pathway

the Absent In Melanoma 2 (AIM2) inflammasome. AIM2 inflammasome–mediated defenses can be blunted by multiple tumor viruses, by other viruses, by bacterial infections,[16] and by many breast cancer mutations as well (Fig. 1 and Table 3).

MyD88 (myeloid differentiation primary response 88) is an adaptor for Toll-like receptors (TLRs) on the cell and endosomal membrane and is essential to produce inflammatory cytokines and Interferons (IFN; Fig. 2). The RTA protein (the transcription activator and lytic switch) from the HHV-8 virus degrades MyD88 and blocks TLR signaling (Fig. 2). HBV and HCV also inhibit MyD88 and alter its downstream signaling.[17,18] Other viruses also target

MyD88. Breast cancer mutations in MyD88 itself were not found, but breast cancer mutations affected many of the steps downstream of the MyD88 gene product (Fig. 2). IRAK2 and IRAK3 (Interleukin 1 Receptor-Associated Kinases) are mutated in different breast cancers, damaging the control of inflammatory cytokine production (Fig. 2). IRAK3 interacts with IRAK2 and inhibits IRAK2-mediated phosphorylation of eIF4E, establishing a connection with protein translation. This prevents translation of inflammatory cytokines and downregulates TLR responses.[19] These genes are associated with multiple infections (Table 3).[20]

The endosomal TLR3 gene has missense mutations in two breast cancers (Table 3). In endosomes (green circle in Fig. 2), TLR3 binds tumor virus double-stranded RNA (dsRNA) such as those from lysed pathogens and activates signaling to the nucleus to produce antiviral cytokines such as IFNs (Fig. 2).[21,22] TLR3 is essential to respond to other viruses listed in Table 3.[9]

RIG-1 (retinoic acid–inducible gene 1–like helicase) is a cytoplasmic recognition sensor for viral RNAs, and RIG-1–mediated pathways attract both mutation and infection (Fig. 2 and Table 3). Multiple infections and breast cancer mutations focus on RIG-1–mediated signaling (Fig. 2).

Twenty mutations in 17 different breast cancers involved dynein heavy chains (Table 3), which transport cargo along microtubules and maintain cytoplasmic architecture. Innate cellular defenses against retroviral infection include restriction factors such as Tripartite Motif-Containing Protein 5 (TRIM5 protein). TRIM5α is present in the cytoplasm, where it interferes with retroviruses shortly after they enter the cell. The restriction factor then inhibits viral uncoating and reverse transcription. The dynein complex is essential to transport TRIM5α protein or complexes containing TRIM5α along microtubules to interrupt cytoplasmic retroviral infections. Crippling the activity of dynein motors or dynein complexes or interfering with microtubule structure decreases the ability of TRIM5α to protect against retroviral infection.[23]

IFNs can transmit signals to the Janus Kinase – Signal Transducer and Activator of Transcription (JAK-STAT) pathway via receptors in uninfected cells[24] to protect them from infection. Abnormal regulation of the JAK-STAT pathway occurs in human cancers in diverse organs[25] and at least seven breast cancers have mutations affecting JAK-STAT signaling (Fig. 2). The JAK-STAT pathway is inhibited by many viruses including Varicella zoster virus (VZV),[26] HBV,[27] and HCV.[28]

Breast cancer mutations interfere with intrinsic immunity. Nonsense-mediated decay (NMD) factors sense premature termination codons associated with translation of some viral sequences. Figure 3 (bottom) shows inhibition or activation of NMD by several viruses. Six breast cancers have mutations in factors required for NMD (Fig. 3 and Table 3).

Infection and mutation can both affect the DNA damage response. Damage to genes encoding pathways to repair DNA damage occurs in at least 18 different breast cancers (Table 3 and Fig. 2). Viral infections can break chromosomes, activating innate immune responses to target infected or transformed cells. Viruses can pervert host DNA repair to promote integration of viral DNA into host DNA and can limit other infections. Chromosomes in virally infected cells can sometimes have a remarkable resemblance to hereditary cancer-prone diseases that have inactive genes required for DNA double strand break repairs. Mutations affecting genomic stability increase infection risks.

The protein signals required for DNA damage responses include ATM, ATR, BRCA1, BRCA2, PALB2, RAD50, RAD51, Fanconi proteins, XPC, and PRKC1. Mutations in many of these genes can be inherited and lead to hereditary cancer predispositions. Chromatid exchanges and aberrations typical of Fanconi anemia and BRCA2 infections can result from viral infections. Mutations in ATM (four breast cancers), BRCA1, BRCA2, and interacting partners (seven breast cancers) and Fanconi proteins (three breast cancers) render the genome less stable by influencing DNA repair. Homozygous ATM mutations are well known to increase infection risks. Table 3 shows infection risks increased by BRCA and Fanconi gene mutations. Breast cancer mutations affecting base excision and nucleotide excision repair pathways also increase risks for infections (Table 3). In turn, infection by *H. pylori*, for one, causes mutations by several mechanisms including downregulating major DNA repair pathways.

Infections associated with mutations affect innate immunity signals. Granzymes are serine proteases without antigen receptors that kill target cells and pathogens directly. Perforin (PRF1) is the chief effector for Natural Killer cell (NK)-mediated cytolysis. Table 3 shows that granzyme and perforin deficits are associated with many infections, both viral and nonviral. Granzyme A (GZMA) and Granzyme H (GZMH) genes are mutated in two breast cancers and PRF1 is mutated in another (Fig. 2, right side).

Damage to genes essential for neutrophil functions. In addition to granzymes, at least 10 other genes (AKT1, AOC3, BIRC6, BPI, CEACAM8, CYBB/NOX2, DBNL, KLK15, MPO, and NCF2) contain mutations that could affect neutrophil effectiveness in 12 different breast cancers. Many infections seen in cancer patients are related to weakened function of neutrophils/phagosome–containing cells. Cancer-causing infections related to the mutations listed above include EBV, HCV, HPV, and *H. pylori*. The CYBB/NOX2 (cytochrome B-245, beta polypeptide) gene mutated in BR-M-045 breast cancer encodes a product that acts in host defense in phagosomes by generating H_2O_2.[29] Multiple noncancer-associated infections are specifically linked to CYBB/NOX2 activity and might exacerbate effects of mutation and of cancer-causing infections.

Breast cancer mutations affecting connections to immune responses and neurological sensing alter risks for infections. In at least 18 of the 103 breast cancers, a gene mutation affects the code for an inflammatory cytokine such as an interleukin (IL). These cytokines are essential signals to activate a long-term adaptive immune response (Fig. 2). Other connections

to innate and adaptive immunity are also damaged including Human Leukocyte Antigens (HLA) or the class II major histocompatibility complex transactivator (CIITA), an important regulator of histocompatibility genes (a total of six breast cancers in Table 3). Damage to these gene products can impair response to a long list of infections. Table 3 also contains many instances of specific individual signals essential for immunity that have sustained serious mutations in their genes. Even a neuroimmune response is damaged when genes encoding taste receptors (TAS1R and TAS2R genes) that sense bacterial endotoxins[30] are mutated in seven breast cancers (Table 3).

Damage to cell adhesion and architecture genes associates with infections. In epithelial cells, CDH1 (cadherin 1, type 1) dynamically complexes with catenins, which regulates signalling pathways such as Phosphoinositide 3 kinase (PIK3)/Akt and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-KB). CDH1 also regulates multiple connections to the innate and adaptive immune systems[31] (Fig. 2). CDH1 gene mutations occur in three different breast cancers, and CDH1 protein is associated with a wide range of infections including some known to cause cancer (Table 3). Maintaining epithelial barriers is a prime immunologic function of CDH1 because it participates in walling off infections and harmful agents to protect underlying structures. Adherens junctions formed by cadherins are known to inhibit lentivirus entry into cells.[32] In all the breast cancers, there were 16 mutations in 13 different cadherins. Many more mutations affected proteins that interact with cadherins.

Cell architecture and structure must be changed in order to accommodate viral infections. Every one of the 103 breast cancers have mutations affecting actin, the cytoskeleton, or its regulation. In order to establish a persistent infection, viruses must escape an immune response and pass through collagen-rich extracellular structures, unfavorable environments, and structural barriers to reach targets.[3,4] Many viruses have evolved the ability to manipulate the actin/membrane network in host cells to facilitate viral replication and then spread to new cells. Over 1/3 (35/103) breast cancers have damage to genes encoding one or more of three families of structural molecules (laminins, collagens, and fibronectin). Collagen alone is dependent on dozens of genes that have mutations in the breast cancers. Defects in these structural proteins could increase susceptibility to a broad range of microbial infections. In addition to viruses, infections that degrade these proteins include gram-positive bacteria, gram-negative bacteria, fungi, anaerobic bacteria, and parasites (Table 4). Vaccinia virus (VACV), *Rickettsia*, and facultative intracellular bacteria *Listeria monocytogenes* and *Shigella flexneri* pervert host intracellular actin to promote transmission to new cells.[33] This suggests that the breast cancer genomes with deregulated cytoskeletal proteins or with considerable damage to the genes encoding cytoskeletal and extracellular signaling connections present many attractive targets for infection either before or after the cancer develops. In this instance, mutation and infection often work in the same direction in breast cancer cells.

Some ion channels have evolved to maintain homeostasis during infections. Because breast and other cancer cells have highly abnormal morphology and size, ion channel mutations may be essential for cancer cells to survive. In many breast cancers, ion channels with known associations to cell volume or morphology are mutated including NEDD4L (Table 3), BEST3, CHRNA9, HBS1L, KCNA4, KCNA5, KCNH4, KCNH8, KCNV2, ACCN1l, TTYH1, and WNK3. Damage to host cell ion channels may facilitate virally enhanced cell permeability caused by incorporation of ion channel proteins encoded by viruses. A growing list of viruses encode their own ion channels (viroporins), including HCV, HIV-1, IAV, Infectious Bronchitis Virus (IBV), poliovirus (PV), Severe Acute Respiratory Syndrome virus (SARS), Sindbis Virus, Semliki Forest virus (SFV),[34] HTLV-1, John Cunningham virus (JCV), and rotavirus.

The gene for intermediate filament–associated protein filaggrin (FLG) was mutated in eight breast cancers (Table 3). FLG aggregates intermediate filaments and helps determine

Table 4. Breast cancers with mutations in major structural proteins that protect against infection.

Structural barrier molecules	Pathogens that produce enzymes that degrade this molecule or adhere to it or Viruses with capsid proteins or antigens that interact with structural barrier molecules[217]	Breast cancers with damage to gene(s) encoding the barrier molecule(s)
Laminins, collagens, fibronectin	Bacteria, fungi, parasites: *Actinobacillus actinomycetemcomitans, Bacillus cereus, Clostridium histolyticum, Clostridium perfringens, Porphyromonas gingivalis, Pseudomonas aeruginosa, P. gingivalis, Streptococcus pyogenes (or group A Streptococcus; GAS), Streptococcus gordonii, Treponema denticola, Vibrio alginolyticus, Vibrio vulnificus, Vibrio parahaemolyticus, Aspergillus fumigatus, Cryptococcus neoformans, C. albicans, Candida spp., Paracoccidioides brasiliensis, Trichophyton schoenleinii, Acanthamoeba castellanii, Acanthamoeba healyi, Balamuthia mandrillaris, Entamoeba histolytica, Giardia duodenalis, Trichomonas vaginalis, Trypanosoma spp.* Viruses: Influenza, HPV, retroviruses, human polyoma virus	BR-M-028, BR-M-037, BR-M-041, BR-M-055, BR-M-076, BR-M-085, BR-M-095, BR-M-098, BR-M-106, BR-M-110, BR-M-120, BR-M-122, BR-M-123, BR-M-126, BR-M-174, BR-M-191, BR-M-193, BR-V-002, BR-V-009, BR-V-014, BR-V-017, BR-V-022, BR-V-023, BR-V-024, BR-V-026, BR-V-027, BR-V-034, BR-V-037, BR-V-043, BR-V-044, BR-V-045, BR-V-047, BR-V-064, BR-V-067, BR-V-071
Actin, actin related	Every virus known interacts with the actin cytoskeleton,[218] *L. donovani, C.trachomatis, salmonella, Borrelia burgdorferi*	All 103 breast cancers. See also reference 4

tissue architecture. Damage to FLG is associated with viral, bacterial, and fungal infections (Table 3). Titin (TTN) is a giant protein with frequent mutations in breast and viral cancers that is important in cytoplasmic and nuclear structure (Table 3). Thirty-four pentamers from a major capsid protein of HPV16 are shared with titin.[35]

Alterations in chromatin structure associated with infections. In the 103 breast cancer exomes, at least 18 mutations in 18 different breast cancers directly affect the structure of one or more histones. Chromatin structure appears to be important in determining the local concentration of mutations, so histone gene mutations may be especially dangerous by improving access to host DNA and facilitating integration of viral genes.

The histone demethylase KDM4A is thought to be essential to maintain HHV-8 in the latent state. HHV-8 inhibits KDM4A, facilitating reactivation. Three breast cancers (Table 3) also inhibit KDM4A by mutation favoring HHV-8 reactivation.[36] MLL genes are histone methyl transferases that are common sites of viral integration. Fourteen breast cancers have mutations in MLL genes, and associations among their mutations exist with five viral infections including four tumor viruses (Table 3).

SMARCA2 and SMARCA4 genes encode components of the SWI/SWF chromatin–remodelling complex needed to activate transcription of some genes. SMARCA2 or SMARCA4 (mutated in four breast cancers) are associated with two cancer retroviruses (HIV-1, HTLV-1) and HPV infection (Table 3). Histone deacetylase mutations in breast cancers can alter chromatin structure and control of numerous infections by reversing acetylation reactions and are crucial for T-cell functions.

Breast cancer mutations affecting transcription and splicing are associated with infection. RNA polymerase III is a sensor for viral infection and is mutated in BR-M-045. Other examples of mutations affecting transcription are listed in Table 3. RNA helicases (DDX genes) are essential for transcription, translation, RNA splicing, RNA transport, and RNA editing. DDX11, DDX20, and DDX47 are associated with HPV and/or EBV infections and are mutated in eight breast cancers. SRRM2 participates in splice site selection and is mutated in four breast cancers (Table 3). SRRM2, a transactivator for HTLV-1 and HIV-1, modulates the alternative splicing complex so that it favors viral replication.[37]

Breast cancer mutations in protein translation pathways are related to infections. Figure 3 is adapted from multiple sources.[13–15] Figure 3 illustrates that breast cancer mutations and infection have clear relationships based on the protein translation pathway steps affected. The steps targeted by mutation versus the steps targeted by infection are either identical or closely related. Hundreds of mutations affect the same pathways as viral and bacterial infections, and the figure shows potential complexities in a network of possible cooperation or antagonism between infections and DNA mutations. Virulence factors in the bacteria, MTb, Shigella, and salmonella (Fig. 3) possess t-RNA nucleases that have the ability to reprogram translation initiation and global translation regulation.[38]

Figure 3 further shows a few of the many connections between these translation pathways and the host immune response (yellow boxes). A PI3K signaling pathway that controls a rate-limiting step in protein translation and the figure shows these steps in green boxes. Links connect this pathway to innate immunity via the TLR3 receptor for innate immunity and the CDH1 receptor (Fig. 2). Thirty-three breast cancers have a mutation that could affect PI3K and six breast cancers have mutations that could affect Akt activity in this pathway. PI3K is stimulated by tumor and other viruses (Table 3).[39] PIK3 enzymes are also stimulated with ligands that activate TLR signaling so PI3K activation can be part of an innate immune defensive response to infection (Figs. 2 and 3). Infections and other mutations shown in Figure 3 can also affect steps prior to PI3K stimulation.

mTORC1 serves as a central regulator of cell growth and division, coordinating signals from diverse processes including immunity, growth factors, nutrients, energy availability, redox status, lipid, nucleotide, and protein biosynthesis. mTORC1 signaling is sensitive to the presence of amino acids, insulin, and translocation to the lysosome.[14,15] In the immune system, mTORC1 exerts extensive control over effector and memory differentiation of peripheral CD4 and CD8 T-cell effector functions. Invariant natural killer T cells, which bridge innate and adaptive immunity, are also controlled by mTORC1 signals and RPTOR as indicated in Figures 2 and 3.[40,41] Control of mTORC1 must be acute and active as determined by the Tuberous sclerosis (TSC1–TSC2) complex,[14,15] but the control becomes deregulated in two breast cancers (Fig. 3) and in some viral infections such as HTLV-1.[42]

EGFR (a receptor tyrosine kinase) is often dysregulated or mutated in breast cancer and a mutation in EGFR itself occurs in four breast cancers (Fig. 3). EGFR itself is a co-receptor for HCMV and AAV6,[43] so EGFR mutations may affect susceptibility to these infections. However, the EGFR network exerts control over cell proliferation, protein translation, cell architecture, and survival, and so hundreds of mutations in the 103 breast cancers would have further impact on the ability of viruses to take over tightly regulated EGFR processes. Many viruses seize control over EGFR endocytosis or signaling to enter host cells, replicate, and evade immune responses (Table 3).

The removal of proteins after translation may be as tightly controlled as their production. F-box proteins are subunits of ubiquitin ligases that identify protein substrates for breakdown by the 26s proteasome. Twelve mutations in F-box proteins occur in the breast cancers giving viruses a head start in subverting protein removal. Several additional mutations more directly affect the proteasome (Fig. 2).

Breast cancer mutations affecting the cell cycle can be associated with infection. Table 3 includes examples of mutations affecting

the cell cycle that have known effects on infection. WEE1 (WEE1 G2 checkpoint kinase) normally coordinates the transition from DNA replication to mitosis. WEE1 is elevated on HHV-6 infection and arrests the cell cycle.[44] WEE1 mutation in three breast cancers prevents cell cycle arrest, disabling this defense mechanism against infection. Cell cycle arrest in infected cells is a major host defense against infections.[45] Other examples include the LATS2 (large tumor suppressor kinase 2) gene and protein phosphatase 2A (Table 3).

Gene mutations affecting metabolism can be associated with infection. Many breast cancer mutations encode proteins that affect metabolism such as glycolytic enzymes, lipid biosynthesis, tissue-repair mediators, and NF-KB. There are often clear signaling connections to the immune system. Aerobic glycolysis controlled by an AKT-mTORC-HIF-1a pathway is the metabolic basis that enables myeloid cells to protect against secondary infections.[46]

The breast cancer BR-M-079 has a mutation that causes the NR1D1 gene to begin transcription out of frame. NR1D1 (nuclear receptor subfamily 1, group D, member 1) encodes for a core member of the circadian clock emerging as a regulator of the immune response and metabolic pathways. The NR1D1 gene product is involved in the response to several microbes (Table 3).[47] Even the prion disease Creutzfeld-Jakob disease[48] is increased by mutation in phospholipase PLCXD3 (lipid catabolism and signal transduction), which is mutated in BR-V-011.

Discussion

Different breast cancers contain mutations that alter responses to microbial infections, and microbial infections can alter responses to mutations and suppress the immune system. Even infections that are not directly linked to cancer may exacerbate damage from mutations and from other infections that do cause cancer. It is likely that there are many more mutations associated with infection because many mutations that affect the immune system have not been studied in the context of risks for infection (Fig. 1). The goal of the present work is the ability to scan mutations in genomes for altered responses to a wide variety of infections. This can be done in few seconds. An emerging list of infection–mutation associations is readily scalable to routine human cancer genome analysis and may be helpful to determine infection susceptibility in other human genome analyses as well.

Mutation of the genes for host regulatory proteins can damage their control by the host, yet help infections bypass host regulatory circuits. This represents an alternative to the view that mutations cause cancer independently from infections. Instead, mutations caused by environmental or genetic damage increase the risks from both bacterial and viral infections and vice versa. One infection can increase damage from another or help control it. Genes encoding the signals needed to perform immune functions and to maintain cell barriers against infection represent most of the gene mutations found in this work and in hundreds of breast and other cancers.[3,4,49] Mutations in other host genes such as those encoding translation are not normally considered as part of innate immunity, but there are multiple and very clear connections. Mutations in host genes controlling rate-limiting steps in translation have clear connections to immune defenses and innate immunity but are not normally considered as antiviral defenses.

Based on Figures 2 and 3, it is difficult to imagine that infections do not participate in the cancer process along with mutations. Infections interfere with corrections of errors; removal of damaged cells; immunity to known cancer viruses; control of the cell cycle, cell size, and shape; cell adhesion; cell metabolism, etc. Signaling pathways that are known to be involved in producing cancer are inhibited or damaged by infections as well as by mutations. In treating cancers, effects from infections should probably be considered along with effects from mutations. The population of cancer patients[50] included in this study contained nine patients with precancerous lesions such as DCIS. Patients with DCIS were not specifically identified in the original DNA sequencing report,[50] but all 103 patients, even those with only a few mutations, had associations with infections. These associations persisted despite the large range in age of the population of female sporadic cancer patients (31–92). There were differences as well in common tumor markers such as estrogen receptors, progesterone receptors, and HER2 status.[50] Moreover, there are probably many more mutation–infection associations because Figure 1 shows that thousands of mutations with likely associations could not be evaluated.

Infections such as HPV and EBV are known cancer viruses that are almost universal in the human population. Patient populations from the developing world who contributed the DNA sequences are at high risk from hepatitis viruses. Mutations that interfere with the control of these known cancer-causing infections would be reasonably expected to increase the number of cancers caused by these infections. High-risk gene mutations in BRCA1 and BRCA2 may have clear links to infection. In prophylactic tissue removed from high-risk BRCA1/2 patients, signs of infection are present even when there are no signs of cancer (B. Friedenson, unpublished observation). Histology photos of breast cancer cells suggest that they are often infected. Many breast cancers contain what look like hollow cells with gutted cytoplasm, a zone of clearing around the nucleus, changes in the cell cytoskeleton, and damage to primary cilia. Breast cancer cells also often contain other signs of viral infection: nuclear and cytoplasmic inclusion bodies, altered shapes, strangling of cytoplasm causing tentacles and projections, and chromatin redistribution or margination (B. Friedenson, unpublished observation).

Defenses against microbial infection are multilayered and depend on exposure and the condition of the immune system. Cancer gene mutations gather on common functions needed to control pathogens, so mutations create gaps in defenses. Responses to pathogens requiring multiple diverse host genes and proteins suggest how mutations could contribute to cancer

in infected individuals and how specific groups of infections might contribute to cancer in populations with particular gene mutations. In most cases, the gene with a mutation was essential to prevent the infection or was required in order for the infection to proceed. This argues that many infections cannot be due to random associations between mutated genes and microorganisms. Despite the above arguments, some infections probably occur after the cancer has developed and could represent cancer symptoms.

A practical application of this new genomic and structural evidence is that it may be feasible to eradicate occult infections and perhaps compensate for some gaps in immune defenses. Vaccinations against likely potential infections may be possible and helpful. Breast cancer cells with their damaged genes are easier to infect with some microbes than cells that do not have damage to the same genes. Therapy with oncolytic microbes that can take advantage of the deficits in breast cancer cells may destroy them with minimal damage to normal cells.

Many viral proteins target host proteins that have major impacts on the cell cycle of host infection targets. Viral proteins also target major regulatory proteins such as p53, RB, and the anaphase-promoting complex via diverse mechanisms.[51] Short stretches of viral protein amino acids (short linear motifs of 3–10 amino acids)[52] interact with such major host regulatory proteins. Short viral interacting sequences are abundant in the human proteome. They make viral interactions with critical host proteins much less specific and much less sensitive to host gene mutation than the complex processes that normally regulate host cells.

Tables 1–4 suggest that altered responses to multiple infections seem to be the rule. The presence of weakened defenses in the face of large numbers of possible infections may factor into explanations for why cancer cells become resistant to targeted therapies. Removal of cancer cells related to one set of infections/mutations may clear the way for cancers associated with alternate different infections/mutations. Targeted therapy then clears the way for competing infections in the group of abnormal vulnerable cells so targeted therapy may fail. The diversity of exome mutations and infections that can potentially participate in carcinogenesis shows that cancer therapy should not consider cancer as a single-gene disease.

At least four well-studied cancer viruses (EBV, HBV, HCV, and HPV) are all represented equally in Table 1. HIV-1 occurs about 50% more often and *H. pylori* about half as often. HPV cancer is thought to be stimulated by coexisting infections such as chlamydia and HSV-2. Figures 2 and 3 show abundant opportunities for more than one infection to become involved in cancer. Breast cancers share the same fraction of their gene mutations with HPV viral cancers of the cervix and with small-cell lung cancer,[4] a "non-viral" cancer attributed to smoking in almost all cases.[53] The results shows that multiple infections can be associated with breast cancers depending on the mutations present. DNA sequencing and microorganism associations were not randomly selected from the general population of breast cancer patients. Thus, the idea that these particular microorganisms are associated in general with breast cancer in roughly these proportions would depend on the mutations and exposures to infection within the population. This requires further study.

The disease stage and type of cancer were not controlled in the 103 breast cancers so infection–mutation associations cannot yet be assigned to any specific stage of the disease. The present study was also quite small but should be easy to expand to larger groups. Another limitation is that the results are biased by the amount of study that each mutation–infection association has received so that genes or infections having the greatest interest are more likely to be represented. The number of infections that can potentially infect humans is probably close to limitless, but there are only a finite number of critical infections in the groups of breast cancer patients from Mexico and Vietnam.

Damage to host cell–protective signals account for high percentages of mutations found in breast cancer cells but must be rationalized with the widely held belief that ≤10 mutations are sufficient to cause cancer and that additional mutations occur as time passes.[54] However, the vast differences in the numbers of mutations in a series of breast cancers show no relationship to the age of the patient,[55,56] suggesting vastly different mutation rates. Evidence supporting ≤10 mutations comes largely from experiments using relatively homogeneous cell cultures that contrast with heterogeneous cancers. Highly important and significant advances have resulted from cancer cell culture experiments, and cancer cell cultures are an invaluable resource. However, relying only on events within a single cell might limit the conclusions. In cell culture, there are only fragments of an immune system; natural protection is largely gone against infection or against abnormal cells; many anatomical and cellular barriers to infection are removed and important protective interactions with the extracellular matrix are not possible. Nonetheless, antibiotics and sterile technique preclude infection. In many experiments, architectural barriers within the cell to cancer-causing infections are overcome by forcible DNA transfection. Normal host cells in a culture without systems that protect from cancer-causing infections may require far fewer mutations to develop cancer. Moreover, cancers strategically placed in the immune system may require fewer mutations than other cancers because the malignancy itself impairs immunity. The success of the drug Gleevec for CML with reciprocal translocated chromosome fragments, has not been widely duplicated in other cancers, suggesting that most cancers are different from CML.

Conclusions

Many mutations in breast cancer alter susceptibility to infection. Change in infection susceptibility is a common thread connecting cancer mutations in diverse functions. Infections and mutations can both contribute to cancer because they deregulate the same pathways. Interventions may be possible to prevent infections from cooperating with mutations to cause further cancer, metastasis, or other complications.

The emerging list of infection–gene mutation associations is readily scalable to routine testing of large human data sets.

Gene Symbols

A useful nomenclature resource for current gene names and gene symbols is Entrez Gene. The HUGO Gene Nomenclature Committee (e-mail: hgnc@genenames.org) and http://www.genenames.org provide human gene symbols.

Microorganism Abbreviations

AAF, Adeno-associated virus; ADV, Adenovirus; AEV, African Epidemic virus; AFSV, African swine fever virus; BHV-1, bovine herpesvirus-1; BLV, bovine leukemia virus; CHIKV, Chikungunya virus; CVB3, Coxsackie virus; DENV, Dengue virus; EBV, Epstein-Barr virus; ECHO30, Echovirus30; EMCV, encephalomyocarditis virus; FV, Foamy virus; HBV, Hepatitis B virus; HBE, hepatitis E virus; (H) CMV, (Human) cytomegalovirus; HCV, Hepatitis C virus; HERV, Human endogenous retrovirus; HEV71, human enterovirus 71; HPV, human papilloma virus; HHV-8, human herpes virus type 8/Kaposi sarcoma associated herpes virus; HIV, Human immunodeficiency virus; hMPV, human metapneumovirus; HSV, Herpes simplex virus; HVS, herpesvirus saimiri; HMPV, human metapneumovirus; HPIV3, Human parainfluenza virus type 3; BKV, Human polyomavirus BK; HTLV-1, Human T-cell leukemia virus; IAV, Influenza A virus; JCV, John Cunningham virus; JEV, Japanese encephalitis virus; KSHV, Kaposi sarcoma-associated herpesvirus; LCMV, murine lymphocytic choriomeningitis virus; MDV, Marek's disease virus; MCPyV, Merkel cell polyoma virus; MHV-08, Mouse hepatitis virus; MMTV, Mouse mammary tumor virus; MV, Measles virus; MHV68, murine gammaherpesvirus68; MLV, murine leukemia; MTb, mycobacterium tuberculosis; NDV, Newcastle disease virus; NiV, Nipah virus; OROV, Oropouche virus; PV, poliovirus; RVFV, Rift valley fever virus; RSV, Respiratory syncytial virus; RV, rhinovirus; SV-A, salivirus A; SeV, Sendai virus; SFV, Semliki Forest virus; SIV, simian immunodeficiency virus; TBEV, tick borne encephalitis; TGEV, transmissible gastroenteritis virus; TMEV, Theiler's murine encephalomyelitis virus; TTVs, Torque teno viruses; VACV, Vaccinia virus; VSV, Vesicular stomatitis virus; VZV, Varicella zoster virus; WNV, West Nile virus.

Author Contributions

Conceived and designed the experiments: BF. Analyzed the data: BF. Wrote the first draft of the manuscript: BF. Contributed to the writing of the manuscript: BF. Agree with manuscript results and conclusions: BF. Jointly developed the structure and arguments for the paper: BF. Made critical revisions and approved final version: BF. Author reviewed and approved of the final manuscript.

Supplementary Material

List of mutations in breast cancers vs associated infections.

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