Protective Innate Immune Variants in Racial/Ethnic Disparities of Breast and Prostate Cancer

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Abstract

Individuals of African descent are disproportionately affected by specific complex diseases, such as breast and prostate cancer, which are driven by both biological and nonbiological factors. In the case of breast cancer, there is clear evidence that psychosocial factors (environment, socioeconomic status, health behaviors, etc.) have a strong influence on racial disparities. However, even after controlling for these factors, overall phenotypic differences in breast cancer pathology remain among groups of individuals who vary by geographic ancestry. There is a growing appreciation that chronic/reoccurring inflammation, primarily driven by mechanisms of innate immunity, contributes to core functions associated with cancer progression. Germline mutations in innate immune genes that have been retained in the human genome offer enhanced protection against environmental pathogens, and protective innate immune variants against specific pathogens are enriched among populations whose ancestors were heavily exposed to those pathogens. Consequently, it is predicted that racial/ethnic differences in innate immune programs will translate into ethnic differences in both pro- and antitumor immunity, tumor progression, and prognosis, leading to the current phenomenon of racial/ethnic disparities in cancer. This review explores examples of protective innate immune genetic variants that are (i) distributed disproportionately among racial populations and (ii) associated with racial/ethnic disparities of breast and prostate cancer.

Introduction

The Human Genome Project and the discovery of distinctive genetic variations across patient populations associated with geography has shaped our genetic analysis and improved our understanding of disparities in complex diseases among different populations. In particular, the use of geographic ancestry, defined as the flow of genetic information in distinct populations over time and geography, aids in delineating the genetic variations that could explain observed differences in cancer incidence and progression among various populations. We sought to link innate immune variants with racial/ethnic disparities in cancer by describing examples of genetic variants unequally distributed among ethnic populations, which paradoxically protect against infection but impact cancer incidence and progression.

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Inflammation and Specific Cancers among Individuals of African Descent

Individuals of African descent, as identified by ancestry informative markers (AIM), and those that self-identify as African American, suffer disproportionately from specific forms of cancer, cardiovascular disease, inflammatory and autoimmune disease, and neurologic dysfunction. Complex diseases are affected by both biological and nonbiological factors, and, in many cases, the biological (genetic) contributors to disease disparities are less clearly understood than psychosocial factors such as environment, socioeconomic status, and health behavior. This article explores evidence that protective innate immune variants contribute to racial disparities in cancer, such as those that occur among individuals of African descent, including colorectal cancer (1) and multiple myeloma (2) in both men and women, breast (3) and uterine (4) cancer in women, and prostate, stomach, and lung cancer in men (5). Except for multiple myeloma, all these tissues have a relatively high exposure to infectious agents that require a strong innate immune defense. The complex association between cancer and inflammation is an increasingly active area of research (reviewed in refs. 6, 7). More specialized reviews address the relationship between inflammation and/or innate immunity and breast (8), colorectal (9), prostate (10–12), lung (13, 14), stomach (15, 16), and ovarian (17) cancers. The specific role of innate immunity [and/or members of the Toll-like receptor (TLR)] family as some of the most common representatives) in tumor progression among these cancers has also received attention (12, 18, 19). A meta-analysis consisting of 64,591 patients with cancer and 74,467 controls of European descent demonstrated that 925 sequence variants in 173 innate immune response markers were significantly associated with lung, ovarian, prostate, breast, and colorectal cancer (20). Unfortunately, few observational studies have tested the hypothesis that genomic

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aberrations in innate immune response genes are linked to racial/ethnic disparities of cancer.

Inflammation and Racial/Ethnic Disparities in Cancer

African American women suffer disproportionately from more aggressive forms of breast cancer (21, 22). Both biological and nonbiological factors contribute to this disparity, although the relative impact of these factors on breast cancer morbidity and mortality is a matter of debate (reviewed in ref. 3). Nonbiological factors that contribute to African-American disparities in breast cancer include low socioeconomic status, limited access to health care, substandard living environments, and nutrient-depleted/high-fat diets (reviewed in ref. 23). Nevertheless, several studies indicate that fundamental biological differences are involved in breast cancer health disparities after controlling for differences in socioeconomic status, access to health care/treatment, and delays in treatment following diagnosis (see refs. 24, 25). Breast tumors display a high degree of molecular heterogeneity within and between molecular subtypes, which vary by phenotype and prognosis (26, 27). However, the most aggressive breast cancers (i.e., those most commonly found among African American women) are associated with inflammation (reviewed in ref. 28), and the role of inflammation in breast cancer disparities has become a growing topic of interest (reviewed in refs. 8, 29).

Several lines of evidence are consistent with the idea that variations in innate immune-related genes contribute to breast cancer disparities. First, Elledge and colleagues observed racial disparities in breast cancer survival among Black, White, and Hispanic women that existed only when comparing women who had lymph node–positive, locally advanced, and metastatic breast cancers (30). Second, small-sized breast tumors (<2.0 cm) metastasize more extensively among African American women relative to their European counterpart due to what is described as "intrinsic biological differences," which are indicators of aggressive cancers (i.e., lymph node involvement and distant metastases). Although the source of these differences was not identified, both estrogen receptor status (another marker of breast cancer aggressiveness) and income were ruled out (25). Third, inflammatory breast cancer (IBC) has significantly higher incidence rates and results in shorter lifespans among African Americans compared with European Americans, respectively, based on a meta-analysis of 180,224 patients with breast cancer (23). Similarly, African American ancestry, but not Hispanic ancestry (determined by self-identification) or socioeconomic status, was identified as an independent predictor of poor prognosis among a cohort of 935 women diagnosed with IBC between 1998 and 2002 (31). Finally, ample evidence exists showing that the frequency distribution of gene sequence variants detected in innate (29) and adaptive (32) immunity differs between patients with breast cancer of African and European descent.

Inflammation due to tissue damage or pathogen infection is the result of a coordinated, interdependent protective response that involves both innate and adaptive immunity. Unlike adaptive immunity that requires days to mount a sustained and highly specific inflammatory response, innate immune defense is mobilized immediately. Importantly, the rapid response characteristic of innate immunity can only be achieved by using a predetermined set of genes that code for products immediately capable of responding to pathogens. The heavy dependence of innate immunity on genetic heritability suggests that it is the contribution of innate, not adaptive, immunity to the mechanisms of inflammation that are inherent in complex disease disparities (33). From the standpoint of population genetics, survival requires genetic adaptation in innate immune defense to counteract the high rate of microbial evolution (34). The need for modifications or genetic variation in innate immune defense is consistent with (i) studies that show these genes are under greater selective pressure than any other class of proteins in the human genome (35, 36) and (ii) studies that show this selective pressure is pathogen driven (37, 38). Malaria provides a well-characterized example of selective pressure by a pathogen on the development and diversity of innate immune variants, such as sickle-cell hemoglobin (HbS), in the human genome over time (reviewed in refs. 39, 40). In Africa, the geographic distribution of the HbS variant matches that of malaria (41), and the persistence of HbS in the human genome illustrates a genetic compromise that achieves survival against a deadly infectious agent (*Plasmodium*) at the cost of introducing another pathology (sickle-cell disease). More relevant to racial disparities in cancer is the example of the Duffy antigen/chemokine receptor (DARC), another nonclassical innate immune gene with variants that protect against malaria. *Plasmodium vivax* binds DARC on erythrocytes to gain entry during infection (42). Genetic variants that reduce DARC expression in combination with the Fy(a–b–) phenotype of the Duffy antigen provide protection against *Plasmodium vivax* but are also associated with pathologies that include increased risk of lymph node and distant metastasis and of poor survival in breast cancer (43).

Geographic Origin and Genomic Variation in Innate Immunity

There are classical innate immune gene variations that display patterns associated with geographic origin. First, Lazarus and colleagues resequenced 16 genes coding for pattern recognition receptors (TLRs, etc.) and related molecules among 93 study participants, including 45 European Americans, 24 African Americans, and 24 Hispanic Americans. These investigators found a total of 705 single-nucleotide polymorphisms (SNP) with distinct SNP distribution patterns that differed for each of the three ethnic groups (33). Second, Quintana–Murci and collaborators analyzed full genome sequence variations from the 1000 Genomes Project and found that innate immune genes were under stronger purifying selection than any other protein-coding gene (35). Notably, the diverse functions of these genes included both classical (antigen recognition and response, development, and maintenance of immune cell lineages, etc.) and nonclassical innate immunity (structure, motility and adhesion, regulation via kinases, and transcription factors and other modulators of gene expression).

Additional findings provide further insight concerning the unique characteristics of ancestry-specific innate immune gene expression and variation. First, the Kwiatkowski study

observed that 532 of the 705 SNP variants in the study (75%) had higher frequencies in African Americans, although only 24 of 93 individuals in the study (26%) had this ancestry. This suggested that a greater haplotype diversity exists within the African American gene pool (44). Two elegant RNA-sequencing studies used monocyte/macrophage cells from individuals of African and European ancestry to explore ancestry-specific transcriptional responses to activation by pathogens or TLR agonists (36, 45). Quintana–Murci and coworkers exposed primary monocytes from 100 Europeans and 100 Africans to TLR agonists LPS (TLR4), Pam3CSK4 (TLR1/2), or R848 (TLR7/8) or to a human seasonal influenza A virus (IAV; ref. 45). In this European study, there was minimal ancestry-related genetic admixture within the two populations. Nevertheless, gene expression in resting monocytes and transcriptional responses to innate immune agonists differed significantly between Europeans and Africans, including 27 innate immune genes that were highly expressed in African but not European monocytes. In a similar study by Barreiro and collaborators, monocyte-derived macrophages from 80 African Americans and 95 European Americans were exposed to *Listeria* or *Salmonella* and were evaluated by expression quantitative trait locus (eQTL) analysis (36). Importantly, this study controlled for ancestry-related genetic admixture common among African Americans and reported results

according to the degree of African ancestry (46). Results indicated a 9.3% ancestry-related difference in gene expression in response to infection, with those of greatest African ancestry demonstrating the strongest inflammatory response, indicated by higher inflammatory gene expression, enhanced bacterial clearance, and other measures (36).

Among innate immune genes, there is a rapidly expanding body of data concerning the 10 human TLRs, their associated molecules (coreceptors, adaptors, regulatory kinases, transcription factors, etc.), and the genetic variants among members of TLR-related pathways. Importantly, TLR pathways have been implicated in cancers that occur disproportionately among individuals of African descent. Although overall TLR function is protective, cross-talk among TLR downstream signaling pathways and other regulatory pathways is complex and nuanced (see ref. 47). As a result, the net impact TLRs have on disease risk and progression is likely to involve multiple genes in one or more downstream signaling axes.

Within the TLR family, the subfamily composed of cell surface TLR2, TLR1, TLR6, and TLR10 recognizes the widest range of pathogen-associated molecular patterns (PAMP) due to the large combination of homo- and heterodimers that can be formed by its members and to the involvement of coreceptors in receptor signaling (reviewed in ref. 48). Population genetics analysis shows that among 63, 47, and 48 individuals
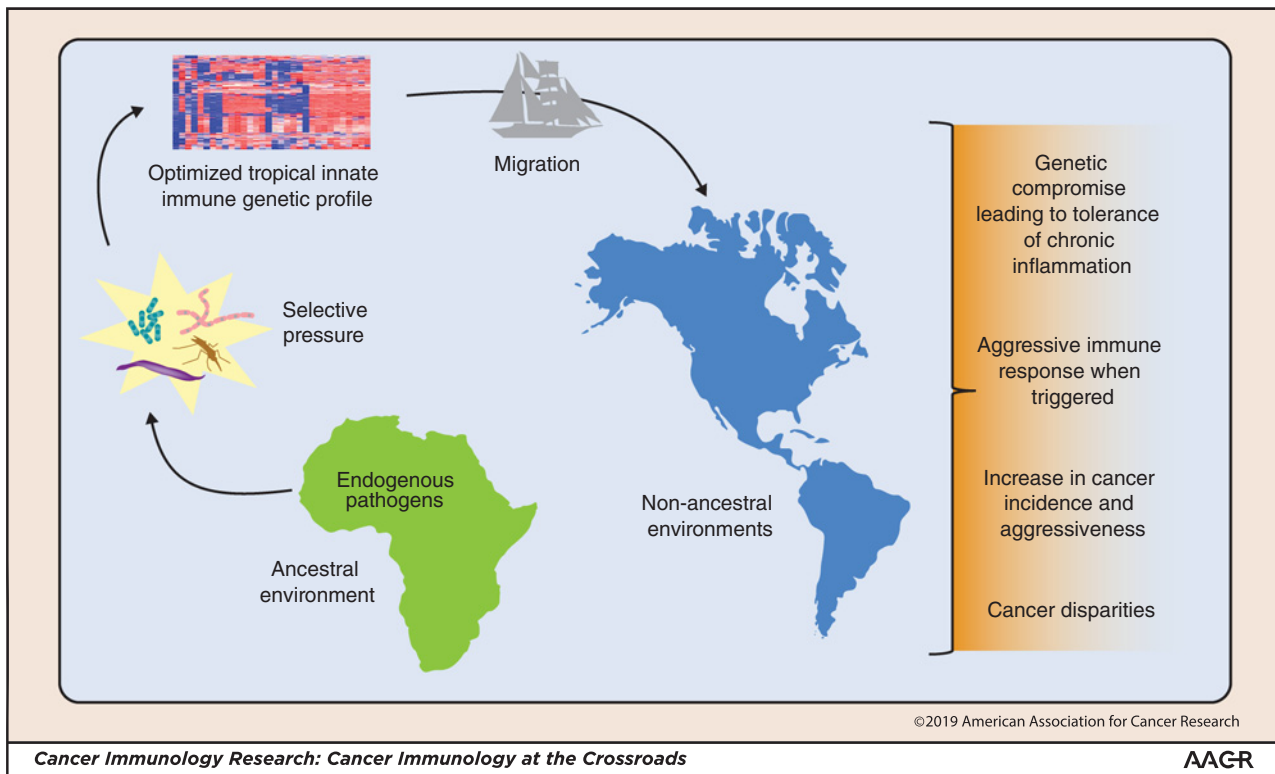

Figure 1.
Geographic origin and effects on racial/ethnic disparities in cancer. Individuals with innate immune gene profiles optimized for pathogen-rich environments (such as tropical climates) are not optimal in all settings and involve genetic compromises in overall immunity, such as tolerance of low-level chronic inflammation and/or hyperaggressive immune responsiveness when triggered, that contribute to the disparate incidence and aggressiveness of specific cancers. The migration of individuals with these innate immune variants from a high-pathogen environment to a new environment results in selective pressure that can change innate immune profiles.

of African, European, and East Asian ancestry, respectively, the DNA sequence diversity of TLR2 (the most commonly paired member of the subfamily) was equally low in all racial groups and lower than that of TLR1, TLR6, and TLR10 (49). In comparison, TLR1 sequence diversity was widely divergent among the three racial groups, with individuals of African descent exhibiting two times more diversity than those individuals of European and East Asian descent. Similarly, individuals of African descent showed greater nucleotide diversity in *TLR6* and *TLR10* genes than those of European or East Asian ancestry (37). Intriguingly, the less well-characterized human *TLR10* gene had the largest sequence diversity among all populations, especially among those of African descent (49). The interaction between two polymorphisms in the TLR2 axis, IRAK4 rs4251545 and TLR2 rs1898830, is a significant predictor of prostate cancer risk among African American men (50). In contrast, when tested in a Swedish cohort as one of 99 SNPs (that did not include TLR2 rs1898830) among 20 TLR pathway genes, IRAK4 rs4251545 did not significantly impact prostate cancer mortality (51). IRAK4 rs4251545 alone is also associated with breast cancer risk among a small cohort of African American women (52).

Ribonuclease L (RNASEL) functions in IFN-mediated antiviral responses, in part, by degrading viral RNA. Nucleic acid–sensing TLR3, TLR7, TLR8, and TLR9 differ in their ligand specificity, with only TLR7 and TLR8 capable of binding single-stranded RNA fragments generated by RNASEL. An intriguing small study noted that the presence of the RNASEL rs486907 variant on one or both alleles strengthened the association between increased fatty acid consumption and prostate cancer risk among Caucasian men, although no mechanism for this association was proposed (53). In contrast, although the sample size was too small to draw conclusions, the data suggest that fatty acid consumption reduces prostate cancer risk in African Americans; however, any association with the RNASEL rs486907 variant in this population could not be addressed. Four studies have evaluated the impact of three RNASEL sequence variants (rs486907, rs56250729, and rs627928) in relation to prostate cancer risk. Two independent observational studies and two pooled analyses revealed that inheritance of the RNASEL rs486907 1385 G>A (Arg462Gln) variant allele was not significantly related to prostate cancer (54–57). However, upon stratification by racial/ethnic group, Liu and coworkers revealed the RNASEL rs486907 GG+GA genotype was protective for African Americans in a pooled analysis of 16 studies (57). Notably, this meta-analysis excluded four additional case–control studies from African Americans, Jamaicans, Caucasian Hispanics, and Caucasian non-Hispanics (54, 58, 59), which compromised the investigators' capacity to generate risk estimates for Caucasian Hispanics and non-Hispanics. This study limitation was resolved in another meta-analysis that demonstrated a marginal increase in prostate cancer risk linked with the RNASEL rs486907 AA genotype among Caucasian Hispanics and African Americans/Afro-Caribbeans when compared with GG+GA carriers (55). Although the three RNASEL sequence variants (rs486907, rs56250729, and rs627928) did not modify prostate cancer risk among Hispanics from Spain, possession of rs486907AA and rs627928 GT/TT genotypes were linked to increased risk for high tumor stage and/or disease progression relative to the referent genotype (56). Although our lab did not establish a link between the RNASEL rs486907 SNP and the risk of developing prostate cancer in a pooled analysis between African Americans and Jamaicans, we did observe a marginal 2.1-fold increase prostate cancer risk among Jamaicans under the heterozygous genetic model (60). Our findings and those of Alvarez–Cubero and coworkers require confirmation in larger racially diverse studies (56). Overall, mixed genetic findings may be attributed to (i) failure to stratify results by ethnicity or genetic ancestry; (ii) differences in the selection of control methods (i.e., population vs. hospital based) used for allelic discrimination; (iii) failure to consider basic confounders (i.e., age, family history, and other prostate cancer risk factors) and effect modifiers [i.e., diet, body mass index (BMI), physical activity, exposure to environmental/inflammatory insults]; (iv) studies with small sample sizes that are underpowered to detect true differences; and (v) variations in study designs.

Future Directions

Individuals from environments that include a dense, diverse, and deadly range of pathogens, such as those of African descent, require robust innate immune genetic programs that, from an overarching perspective, might be expected to tolerate a relatively high background of microbes and other environmental insults but respond rapidly and aggressively to legitimate threats. However, whether the innate immune program is defending against malaria or promoting tumorigenesis, it is becoming increasingly clear that an effective response must be profoundly nuanced, given the capacity for both *Plasmodium* (61) and cancer (62, 63) to subvert immune defense strategies. Gene expression analysis of breast and prostate cancers indicates the existence of distinct immune profiles among groups of individuals who vary by geographic ancestry (Fig. 1; refs. 64–66). Consequently, it is predicted that racial differences in innate immune programs will translate into ethnic differences in both pro- and antitumor immunity, tumor progression, and prognosis (67, 68), leading to the current phenomenon that African Americans acquire earlier onset and more aggressive breast (25, 69) and prostate cancers (5). It is these genetic variations in the innate immune system that suggest the need for intense scrutiny in identification and targeting of novel immunologic therapies and their efficacy in racial/ethnic populations. Such consideration will guarantee that immuno-oncologic findings are impactful to all population groups, thus reducing and eventually eliminating racial/ethnic disparities in cancers.

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