

## ■ CARCINOGENESIS

**Breast Cancer Risk May Be Linked to Genetic Variants of the Mannose-binding Lectin 2 Gene**

Bernig T, Boersma BJ, Howe TM, Welch R, Yadavalli S, Staats B, Mechanic LE, Chanock SJ, and Ambis S. The mannose-binding lectin (*MBL2*) haplotype and breast cancer: An association study in African-American and Caucasian women. *Carcinogenesis* 28: 828–36, 2007.

**E**arly observations of cancer patients who had fully recovered from an acute bacterial infection suggested that innate immunity has antitumor activity. Today, we know that activation of innate immunity can lead to the elimination of cancer cells through cellular mechanisms such as complement-activated lysis and C3b-mediated phagocytosis.

Innate immunity depends on both pattern-recognition receptors and the complement system for target recognition. Innate pattern recognition receptors are ubiquitously expressed by immune and non-immune cells and recognize pathogen-associated molecular patterns. Among these receptors, toll-like receptors are currently of interest in cancer biology because of their altered expression in tumors and their ability to activate NF- $\kappa$ B and inflammatory responses. The major role of the complement system is to promote clearance of invaders and altered host cells. In this function, complement aids the tumor-specific T-cell response in the elimination of cancer cells.

Complement activation leads to the liberation of pro-inflammatory factors and the activation of inflammatory cells, which may have pro-carcinogenic effects. This mechanism could have significant implications for breast cancer because tumor-infiltrating phagocytes and pro-inflammatory cytokines have been found to augment angiogenesis and breast tumor invasiveness. Proteomic studies have identified complement component 3 (C3)–derived peptides as candidate breast cancer serum markers, and both C3 and natural killer cells are regulated by estrogen receptor  $\alpha$ . Cell surface deposition of C3 in breast tumors has been observed, and cell membrane proteins that prevent complement-mediated cell toxicity, such as CD46, are expressed in breast tumors. It is surprising how little attention has been paid to the analysis of complement resistance in tumor cells or to ways that this phenomenon might be targeted in cancer therapy.

Complement activation proceeds through three different pathways that converge in the activation of C3. Activation of complement by lectin is crucial for innate immunity and is driven by the mannose-binding lectin (MBL) protein. This relationship has been revealed by analysis of common single nucleotide polymorphisms (SNPs) in the *MBL2* gene, which

encodes MBL. The frequency of SNP-determined MBL deficiency is significantly higher in patients presenting with various infections and autoimmune disorders than it is in the general population, indicating the importance of MBL in host defense.

MBL is a plasma protein of hepatic origin. SNPs in exon 1 of *MBL2*, known as the B-, C-, and D-alleles, alter the functional properties and circulating levels of MBL protein. They create, together with three linked promoter polymorphisms (known as H/L, Y/X, and P/Q), several well-characterized haplotypes that strongly influence complement activation. The prevalence of *MBL2* variations is associated with race/ethnicity; the variant B allele occurs in approximately one of four Caucasians, whereas the variant C allele is common in the sub-Saharan African populations.

We investigated the association of *MBL2* genotypes with the risk of developing breast cancer and comprehensively analyzed the genotype and haplotype of 26 *MBL2* SNPs in a case-control study of breast cancer. We found that an SNP in the 3' untranslated region (UTR) of *MBL2* (rs10824792) was associated with an approximate 50% reduction in breast cancer risk in African American women but not Caucasian women. Haplotype analysis of *MBL2* showed that the frequency of the corresponding 3' haplotype was also significantly lower in breast cancer patients than in controls among African American women. Our study suggests that a common genetic variant in the 3' UTR of *MBL2* may reduce the risk for breast cancer in African American women, probably through an interaction with the 5' secretor haplotypes that are associated with high concentrations of MBL.

Because these are preliminary findings, we interpret them with caution. Future studies are required to corroborate the relationship between the 3' UTR haplotype of *MBL2* and breast cancer. It is plausible, however, that *MBL2* genetic variants modify the risk of breast cancer in one race/ethnic group but not in another. The *MBL2* haplotype structure is very different between African Americans and Caucasians. MBL also may interact with other breast cancer risk factors that are more common in the African American population than in Caucasians. MBL is found in complexes with four structurally related proteins, the MBL-associated serine proteases (MASPs) 1, 2, and 3 and Map19. Functionally, the protein complex between MBL and MASP-2 is the most significant. Because the *MASP-2* gene harbors several allele variants whose frequency varies widely among different race/ethnic groups, the association of *MBL2* variants with breast cancer is possibly influenced by *MASP-2* gene polymorphisms in a race/ethnicity-dependent manner.

Our study was not the first to observe an association between *MBL2* genotypes and human cancer. A recent case-control study of stomach cancer found a significant association between an increased cancer risk and the HYD haplotype of *MBL2*, which encodes a functionally impaired MBL protein and results in lower protein serum levels (Baccarelli A et al. *Int J Cancer* 119: 1970–5, 2006). Thus, additional evidence exists that MBL function contributes to human cancer risk. Although these findings require verification by other studies, future research should investigate the implication of *MBL2* genetic variants in response to therapy and disease outcome.

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