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Genetic Variation in Immunosuppressive Pathways and Breast Cancer Susceptibility and Prognosis

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Immuno-evasion, implicating tumor cells that acquire the ability to evade the host anti-tumor immunity, has been suggested as a new hallmark of cancer in the last decade. FOXP3+ regulatory T cells (Treg cells) and myeloid derived suppressor cells (MDSCs) have been recognized as two major components involved in immunosuppression in the tumor microenvironment. Genetic variation in the immunosuppressive pathway, i.e. Treg cells and MDSCs relevant genes, could contribute to women breast cancer, but had not yet been broadly investigated and discussed at the time this thesis was initiated.

To investigate associations of genetic variation in the immunosuppressive pathway and breast cancer susceptibility and prognosis, the main hypotheses of this thesis were that inherited common variation in genes of the immunosuppressive pathways, including Treg cells and MDSCs: (1) could be associated with breast cancer susceptibility, possibly different for subgroups of breast cancer, and/or (2) could modulate response to adjuvant chemotherapy, particularly among estrogen receptor (ER) negative breast cancer patients. A total of 133 candidate genes in the immunosuppressive pathway was selected and included.

Briefly, 3,595 single nucleotide polymorphisms (SNPs) were analyzed for their associations with breast cancer risk among 42,510 cases and 40,577 controls pooled from 37 BCAC (Breast Cancer Association Consortium) studies, and 3,610 SNPs were assessed for their associations with breast cancer survival among 11,668 patients with invasive tumors from 16 BCAC studies. Per-allele associations were estimated using multivariable logistic regression model and Cox proportional hazard regression model in the risk and survival analysis, respectively. In addition, principal component analysis and the Gamma method were applied to combine information across a gene or the overall pathway to determine a global association for single genes or the pathway. Multiple comparisons were accounted for using the Bonferroni correction method.

In the risk analysis, per-allele effects of polymorphisms in the immunosuppressive pathway provided evidence that genetic variants in the *TGFBR2* (3p22), *STAT3* (17q21.31), *TGFBR3* (1p33-p32), and *CCND1* (11q13) genes may be significantly associated with breast cancer susceptibility. Although *TGFBR2* and *CCND1* had been identified as susceptibility loci of breast cancer in previous genome wide association studies or fine-mapping studies, a possible independent susceptibility allele in *TGFBR2* was found. Additionally, gene-specific association results supported that of single SNP associations, suggesting that *STAT3* could be a novel breast cancer susceptibility locus. However, further independent replication analyses and functional studies are necessary to draw a more convincing conclusion for this locus.

In the survival analysis, assessment of associations with breast cancer survival revealed that multiple genes, i.e. *TGFBR2* (3p22), *IL12B* (5q31.1-q33.1), *HDAC9* (7p21.1), *CCR9* (3p21.3), *EIF2A* (3q25.1), *PRKCQ* (10p15), and *FLT3* (13q12), may harbor genetic variants associated with clinical outcome of breast cancer subtypes, according to chemotherapy. Particularly, *TGFBR2* rs1367610, together with *IL12B* rs2546892 and rs2853694, were associated with both overall survival and breast cancer-specific survival only in ER-negative breast cancer patients who received adjuvant chemotherapy. The association with *TGFBR2* rs1367610, but not *IL12B* rs2546892 and rs2853694, was replicated using BCAC Asian samples and an independent European population from the POSH study (Prospective Study of Outcomes in Sporadic versus Hereditary breast cancer, United Kingdom). Therefore, *TGFBR2* may have prognostic value for ER-negative breast cancer patients who received adjuvant chemotherapy, providing prognostic and predictive evidence of chemotherapy for ER-negative breast cancer and led to further research on therapy targets.

This thesis mainly focused on common polymorphisms in a candidate pathway without prior knowledge of biological function. Therefore, the present findings provided indications for further functional studies which may elucidate underlying biological mechanisms. Other genes, which did not show significant associations, may also have an impact on breast cancer risk or prognosis, but were disregarded due to stringent correction for multiple comparisons.

In summary, this thesis elucidated that genetic variation in the immunosuppressive pathway may harbor multiple susceptibility loci associated with the etiology and/or clinical outcome of breast cancer in women of European ancestry. Further genetic and functional studies are still required to identify the causal variants and the mechanisms underlying the observed associations.