EVIDENCE OF IMMUNE SUPPRESSION IN PBMC OF PATIENTS NEWLY DIAGNOSED WITH DUCTAL CARCINOMA IN SITU (DCIS)

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Background Ductal carcinoma in situ (DCIS) is considered as a non-obligate precursor of invasive ductal carcinoma (IDC). There is increasing incidence and prevalence of DCIS and recent findings have implicated the tumor immune microenvironment (TME) as the predictor of risk of invasive breast cancer development. We started with the hypothesis that the TME is the whole patient and that some immunosuppressive and immunoregulatory effectors found at the sites of cancer and pre-cancer would also be found in the blood.

Methods We conducted a comprehensive analysis of PBMC from newly diagnosed DCIS patients (n=32) and compared them to PBMC from IDC patients (n=22) and healthy age-matched controls (n=5). We used Flow analysis to identify various immune cell types expressing specific phenotypic markers of immune effectors or immune suppressors including T cell exhaustion markers in different subset of T cells, NK, and NKT cells, as well as FoxP3+ regulatory T cells (Treg), and myeloid-derived suppressor cells (MDSC). High percentages of Treg and myeloid derived suppressor cells have been reported in IDC, as well as high expression levels of exhaustion markers on T cells and other effector cells. This information was missing for DCIS patients.

Results As expected, and in agreement with previous observations in IDC and other cancers, we found statistically significantly higher frequency of exhausted cells in IDC compared to healthy controls. The most prevalent were CD8+ Tim-3+ effector memory T cells (TEM) and terminally differentiated effector memory T cells (TEMRA) as well as CD4+ Tim-3+ TEMRA, NK+LAG-3+, and NK+PD-1+ cells. These cells were still present at healthy control levels in DCIS. However, the frequency of CD8+ LAG3+ and CD4+ PD-1+ TEM and TEMRA were significantly increased in the PBMCs of patients with DCIS compared with healthy controls and IDC. We found additional difference between DCIS and IDC in the statistically significantly higher percentages of FoxP3+ Treg in IDC. MDSC, on the other hand, were equally high in DCIS and IDC. Taken together, these data show the beginning of immune suppression and immune exhaustion at the precancerous DCIS stage that changes and gets worse as IDC develops.

Conclusions We are currently profiling sera corresponding to the PBMC for proinflammatory and other cytokines and chemokines. We are also looking for evidence of humoral immunity to several breast cancer antigens known to be expressed on DCIS and IDC. These data will inform a planned clinical trial of a preventative breast cancer vaccine in the setting of DCIS.

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