TUMOR INFILTRATING PLASMA CELLS ARE ASSOCIATED WITH TERTIARY LYMPHOID STRUCTURES AND PROTECTIVE IMMUNITY IN HUMAN OVARIAN CANCER

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Rationale: Tumor-infiltrating plasma cells (PCs) and their associated autoantibodies are present in ovarian and other cancers, but their contribution to tumor immunity remains poorly understood. In autoimmunity, PCs contribute to antigen spreading to CD4+ and CD8+ T cells, leading to exacerbated tissue destruction. Based on this, we reasoned that PCs might enhance tumor-infiltrating T cell (TIL) responses in cancer.

Hypothesis: Tumor-infiltrating PCs are associated with cytotoxic T cell responses and patient survival in ovarian cancer.

Methods: We used multicolor immunohistochemistry, flow cytometry, and gene expression analysis to study immune responses in three cohorts of high-grade serous ovarian cancer (HGSC) patients.

Results: Approximately 20% of HGSC cases contained PC infiltrates, which constituted up to 90% of cells in tumor stroma. PC infiltrates were associated with tertiary lymphoid structures (TLS), which exhibited germinal centres and other hallmark features of lymph nodes. Tumors containing PC infiltrates had significantly increased densities of CD8+ TIL and were associated with favorable prognosis. Analysis of gene expression data from The Cancer Genome Atlas revealed a two-gene plasma cell signature associated with prolonged survival and expression of genes involved in cytotoxic immune responses, lymphocyte recruitment, PC survival, and TLS formation. This signature was also associated with expression of a greater number of cancer-testis (CT) antigens.

Conclusions: Tumor-infiltrating PCs are associated with increased CD8+ TIL, cytotoxic gene signatures, and CT antigen expression in HGSC. This suggests PCs may serve to amplify cytotoxic T cell responses. We are currently cloning IgG from single sorted PCs to identify their target antigens and to determine whether these are also recognized by CD4+ and CD8+ TIL. A better understanding of tumor-infiltrating PCs and their autoantibody targets may lead to new strategies to enhance CD4+ and CD8+ TIL responses.

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