IGKC and Prognosis in Breast Cancer—Response

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We are appreciative of the comments made by Schmidt and colleagues in a letter responding to our CCR Translations article (1), in which we discussed their data recently published in Clinical Cancer Research (2). The purpose of our CCR Translations was to emphasize the importance of the discovery that the immunoglobulin kappa chain (IgkC) is not only a robust prognostic biomarker in several human solid tumors but also predicts response to neoadjuvant chemotherapy in breast cancer (2). By focusing on the presence of B cells and plasma cells in tumors as well as the role B-cell metagene expression plays in tumor outcome, we did not wish to imply that infiltrating T cells are less important than B cells. Because T cells usually are the major tumor-infiltrating lymphocytes, we were, in fact, surprised that the B-cell metagene showed what we interpreted as a stronger and more robust correlation with metastasis-free survival (MFS) than the T-cell metagene in breast cancer. By pointing to their results, which show that in addition to the B-cell metagene, the T-cell metagene was also associated with MFS by univariate analysis in 3 independent cohorts of breast cancer patients (3), Schmidt and colleagues acknowledge the potential role T cells play in breast cancer prognosis. We certainly agree with this interpretation. The “immune signature” of a growing tumor consists of a complex mix of various immune cells, which interact with the tumor and with each other. Which of these cell types will be more relevant for outcome might depend on the microenvironmental signals that the tumor delivers. Nevertheless, the cooperation between T and B cells (i.e., the cellular and humoral components of the immune response) might be a critical factor that is necessary for favorable outcome. Neither T cells nor B cells alone are likely to prevail in the hostile tumor microenvironment, and the presence of both may be essential for a complete and effective antitumor immune response. This possibility is supported by growing evidence both in experimental models and in clinical settings (ref. 4; Ferris and Ferrone, unpublished results).

As to the “Janus-faced nature” of the humoral immune system, as evidenced by the occasional association of the B-cell/plasma cell metagene with worse prognosis (1), this is not unexpected. B cells can be beneficial or destructive, depending on the delicate balance that exists between the host immune system and the tumor. If the tumor “immune signature” is orchestrated by the tumor-derived signals, as suggested above, the fine balance between T and B cells is disrupted with unpredictable and perhaps dire consequences. It has been known for a long time that components of the immune system are characterized by remarkable plasticity (5). B cells, like T cells, can regulate their own functions and those of other cells. The existence of regulatory B-cell subsets (6), comparable to regulatory T cells, presents us with another piece of a puzzle needed to determine how immune responses are modulated in health and disease. We fully agree with Schmidt and colleagues that a better understanding of cellular interactions at the genetic and molecular levels is critical for improving diagnosis, prognosis, and therapy of cancer.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References


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