For Breast Cancer Prognosis, Immunoglobulin Kappa Chain Surfaces to the Top

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The stromal immunoglobulin kappa chain (IGKC) has been validated as an immunologic biomarker of prognosis and response to therapy in human breast cancer and other cancers. This validation emphasizes the key role of humoral immunity in control of cancer progression and has major implications for determining prognosis of patients with cancer. Clin Cancer Res; 18(9); 1–3. ©2012 AACR.

In this issue of Clinical Cancer Research, Schmidt and colleagues (1) report that immunoglobulin kappa chain (IGKC) RNA levels predict metastasis-free survival and favorable response to chemotherapy in patients with breast cancer. Further, IGKC gene expression is prognostic in non-small cell lung cancer (NSCLC) and colorectal cancer, but not in ovarian cancer. Gene array data from more than 1,800 patients with breast cancer, 1,000 patients with NSCLC, 500 patients with colorectal cancer, and 400 patients with ovarian cancer were evaluated. The results were validated by RNA- and protein-based IGKC expression studies in hundreds of formalin-fixed, paraffin-embedded tissues and by microscopic identification of tumor-infiltrating plasma cells as the source of IGKC. This report is of major importance for cancer biomarkers and clinical tumor immunology fields; a single robust immune marker that lends itself to clinical-scale testing, allowing for prediction of metastasis-free survival and response to chemotherapy, is finally available! The results move immunologic biomarkers into the limelight and provide support for the key role of the immune system in cancer development and progression. To date, a search for promising immune correlates of cancer diagnosis, prognosis, and survival has been largely confined to cellular immune responses. In contrast, this study focuses attention on a component of humoral immunity, the kappa light chain of immunoglobulin (Ig).

The most important feature of IGKC as a biomarker is that it predicts response to neoadjuvant chemotherapy in breast cancer. Markers that help in selection of treatments likely to benefit the patient are desperately needed in oncology. To date, few of these biomarkers have been identified, and none fits in the immune marker category. The introduction of IGKC as a single, easily measurable immunologic biomarker of prognosis and response to therapy in solid tumors fills a major unmet need in clinical practice. IGKC expression can be measured in tissues by immunohistochemistry or PCR, methods that are universally available in pathology laboratories. Thus, it is ready for routine clinical applications, and this opens the way for a broader use of humoral antitumor immunity responses for predicting disease outcome.

The presence of IgG (IgG⁺) plasma cells in breast cancer was first noted in the 1980s (3) and confirmed in the 1990s (4). In this context, the more recent finding by Schmidt and colleagues of the "B-cell signature" consisting of 60 genes in breast cancer was not a surprise (5). Expression of the B-cell cluster of genes containing transcripts for heavy and light chains of Ig (the B-cell metagene), but surprisingly not of the T-cell metagene, in breast cancer specimens of 200 untreated patients had a significant prognostic impact on metastasis-free survival (5). Now, Schmidt and colleagues show that IGKC is as predictive as the entire B-cell metagene (1). IGKC was the strongest discriminator of patients with breast cancer with and without metastases among the 60 genes found in the B-cell metagene (1). This finding greatly simplifies testing, because instead of the whole B-cell metagene, it is now sufficient to probe tissue specimens for expression of only 1 marker gene or protein, IGKC, to obtain an estimate of prognosis or follow responses to therapy.

Because IGKCs, like all Ig molecules, are products of plasma cells, it can be surmised that increased IGKC RNA or protein expression in breast cancer tissues is directly related to increased numbers of plasma cells secreting Ig. This finding, in turn, means that B-cell differentiation takes place in tumor tissues, as confirmed by microscopic images of plasma cells full of intracytoplasmic IGKC in breast cancer tissues (1). Further, the presence of IgM heavy chain transcripts in low-proliferating breast cancer compared with IgG heavy chain transcripts in rapidly proliferating breast cancer suggests that isotype switching associated with the maturation of humoral responses also takes place in tumor tissues (5). Although confirming earlier reports of the plasma cell presence in breast cancer (3, 4), the current
study reintroduces the as-yet unanswered question of whether these plasma cells produce tumor antigen–specific antibodies. Earlier attempts to answer this critical question were inconclusive and failed to link the in situ IgG production to patient survival (4, 6). Now, almost 30 years later, we learn that IGKC expression levels in breast cancer indeed correlate with outcome. The implication is that Ig produced by plasma cells present in breast cancer either directly or indirectly contributes to improved prognosis and that at least some of these Igs are tumor antigen specific. Future identification of these tumor antigens might confirm the cause–effect relationship of the association of IGKC expression levels with disease outcome and provide well-defined targets for antibody-based immunotherapy of malignant diseases. It might also explain why the association has been found in some but not all of the diseases investigated.

Figure 1 illustrates the mechanisms that could be engaged by tumor antigen–specific antibodies to inhibit tumor progression and thus improve outcome. These tumor antigen–specific antibodies are capable of amplifying innate and adaptive cellular immune responses to the detriment of the tumor and, thus, are likely to benefit the patient. The efficacy of cancer immunotherapies with tumor antigen–specific antibodies, such as rituximab, cetuximab, and trastuzumab, is thought to be mediated via antibody-dependent cellular cytotoxicity and/or the inhibition of major signaling pathways (2, 7). These mechanisms may be responsible in part for the current findings identifying IGKC as a robust marker of better prognosis and response to chemotherapy. To date, studies of immune infiltrates in human solid tumors have mainly examined the density and localization of T cells, natural killer (NK) cells, or monocytes, but almost never of plasma cells. The clinical relevance of infiltrates was ascribed to CD3+CD8+ T cells and CD4+CD45RO+ memory T cells. Recently, the realization that the tumor–host interactions are critical for the fate of an individual cancer patient has prompted the reassessment of the role that tumor-infiltrating immunocytes play in cancer progression. Using tools from modern systems biology, Galon and colleagues found that patients with colorectal cancer with a high T-cell density in the tumor have a better prognosis than patients with low T-cell density (8). T-cell infiltrates emerged as the strongest independent prognostic parameter relative to currently used clinicopathologic criteria, such as tumor size, depth of infiltration, and nodal status (9). An independent study by Mahmoud and colleagues corroborated the prognostic significance of “immune tumor signature” in breast cancer (10). The “immune score,” which can predict clinical outcome independently of the tumor type better than the conventional American Joint Committee on Cancer staging system, has been proposed as an alternative classification system for cancer (11). However, the immune score is not yet used in routine clinical practice, possibly because of standardization issues and requirements for automated image analyses. It is interesting to note that the B cells or plasma cells are rarely mentioned as part of the immune score. It is hoped that the results reported by Schmidt and colleagues (1) will encourage consideration of IGKC expression in future studies of the immune signature in solid tumors.

Figure 1. Molecular mechanisms underlying antitumor activities of tumor antigen (TA)–specific antibodies. Tumor antigen–specific antibodies may mediate antitumor effects by inhibiting the function of the tumor antigen they recognize and/or by inhibiting signaling pathways associated with cell survival and/or proliferation (left). Alternatively, tumor antigen–specific antibodies may bind to tumor cells and activate Fc receptors (FcR) bearing NK cells and/or the complement system. These effector mechanisms lyse target cells (center). Lastly, tumor antigen–specific antibodies can trigger or enhance tumor antigen–specific T-cell immunity and amplify innate immune responses (right).
immunity in tumor development, progression, and therapy. This discussion has been exacerbated by recent disagreements about the reasons for poor effectiveness of antitumor immunotherapies (12). To date, the most effective immunotherapies are antibody based. Although T cells are important in cancer control, so are antibodies, and it is the immune system as a whole that is responsible for maintaining homeostasis in health. In disease, including cancer, this homeostasis is disrupted, affecting both humoral and cellular arms of the immune system. Therefore, confining a search for immune biomarkers of cancer prognosis to T cells is short-sighted. The success of IGKC as a surrogate of prognosis in breast cancer and other solid cancers confirms that humoral immunity is as important as T cells in eliminating cancer. With few predictive markers available in oncology, IGKC is likely to play a very significant role in the immediate future.

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