For breast cancer prognosis, immunoglobulin kappa chain surfaces to the top

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Running Title: IGKC and prognosis in breast cancer

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Summary

The stromal immunoglobulin kappa chain (IGKC) has been validated as an immunological biomarker of prognosis and response to therapy in human breast cancer and other cancers. This emphasizes the key role of humoral immunity in control of cancer progression and has major implications for determining prognosis of patients with cancer.
In this issue of *Clinical Cancer Research*, Schmidt and co-authors (1) report that immunoglobulin kappa chain (IGKC) RNA levels predict metastasis-free survival and favorable response to chemotherapy in breast cancer (BrCa) patients. Further, IGKC gene expression is prognostic in non-small cell lung cancer (NSCLC) and colorectal cancer (CRC) but not in ovarian cancer (OvCa). Gene array data from over 1800 BrCa, 1,000 NSCLC, 500 CRC and 400 OvCa patients 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 a limelight and provide support for a 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 neo-adjuvant chemotherapy in BrCa. Markers that help in selection of treatments likely to benefit the patient are desperately needed in oncology. To date, few such biomarkers have been identified (2), 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 fulfills 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. This opens the way for a broader use of humoral anti-tumor immunity responses for predicting disease outcome.

The presence of IgG+ plasma cells in BrCa has been first noted in 1980s (3) and confirmed in 1990s (4). In this context, the more recent finding of the “B-cell signature” consisting of 60 genes in BrCa by Schmidt et al 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 BrCa 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 BrCa patients 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 one marker gene or protein, IGKC, to obtain an estimate of prognosis or follow responses to therapy.

Because IGKC, like all Ig molecules, are products of plasma cells, it can be surmised that increased IGKC RNA or protein expression in BrCa tissues is directly related to increased numbers of plasma cells secreting Ig. This, 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 BrCa tissues (1). Further, the presence of IgM heavy chain transcripts in low-proliferating
BrCa vs IgG heavy chain transcripts in rapidly-proliferating BrCa suggests that isotype switching associated with the maturation of humoral responses also takes place in tumor tissues (5). While confirming earlier reports of the plasma cell presence in BrCa (3,4), the current study reintroduces the so far unanswered question of whether these plasma cells produce tumor antigen (TA)-specific antibodies (Abs). 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 BrCa indeed correlate with outcome. The implication is that Ig produced by plasma cells present in BrCa either directly or indirectly contributes to improved prognosis and that at least some of these Igs are TA-specific. Future identification of these TA might confirm the cause-effect relationship of the association of IGKC expression levels with disease outcome and provide well-defined targets for Ab-based immunotherapy of malignant diseases. It might also explain why the association has been found in some but not all the diseases investigated.

Figure 1 illustrates the mechanisms that could be engaged by TA-specific Abs to inhibit tumor progression and thus improve outcome. These TA-specific Abs 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 TA-specific Abs such as Rituximab, Cetuximab or Trastuzumab are thought to be mediated via antibody-dependent cellular cytotoxicity (ADCC) and/or the inhibition of major signaling pathways (2, 7). These mechanisms may be in part responsible for the current findings identifying IGKC as a robust marker of better prognosis and response to chemotherapy.
Insert Figure 1.

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 and 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 tumor-infiltrating immunocytes play in cancer progression. Using tools of the modern systems biology, Galon and colleagues found that CRC patients with a high T-cell density in the tumor have a better prognosis than those 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 et al corroborated the prognostic significance of “immune tumor signature” in BrCa (10). The “immune score” has been proposed as an alternative classification system for cancer which can predict clinical outcome independently of the tumor type better than the conventional AJCC staging system (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 et al (1) will encourage consideration of IGKC expression in future studies of the “immune signature” in solid tumors.

There has long existed a rift among tumor immunologists as to the role of humoral vs cellular immunity in tumor development, progression and therapy. This has been exacerbated by
recent disagreements about the reasons for poor effectiveness of anti-tumor immunotherapies (12). To date, the most effective immunotherapies are Ab-based. While T cells are important in cancer control, so are Abs, 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 BrCa 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.

References


Figure Legend

**Figure 1.** Molecular mechanisms underlying anti-tumor activities of TA-specific Abs. TA-specific Abs may mediate anti-tumor effects by inhibiting the function of the TA they recognize and/or by inhibiting signaling pathways associated with cell survival and/or proliferation (left). Alternatively, TA-specific Abs may bind to tumor cells and activate Fc receptors (FcR)-bearing natural killer (NK) cells and/or the complement system. These effector mechanisms lyse target cells (center). Lastly, tumor antigen-specific Abs can trigger or enhance TA-specific T-cell immunity and amplify innate immune responses (right).
Tumor cell targeting

Immunological mechanisms

Enhancement of TA-specific and innate immune responses

Signaling blockade
Induction of apoptosis

Inhibition of targeted TA function

Complement

Effector cell

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