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CEBP Celebrates 20 Years: Commentaries
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Harnessing the Immune Response for Cancer Detection

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The development of cancer is a multistep process. The most effective means for eradicating cancer is through detection and eradication of precursor lesions, as is done with removal of polyps to prevent colon cancer. For most cancers, we are challenged by lack of effective means to detect precursor lesions as well as cancerous lesions at an early stage. A strategy yet to be fully exploited stems from the immune response that occurs early during tumor development. Ample evidence exists for the occurrence of genomic alterations in preneoplastic lesions as a consequence of which aberrant expression of proteins may occur that provides a source of antigens that drive an immune response. Thus, identification of antigens that are expressed at early stages of tumor development and that induce a humoral response would lead to the development of simple noninvasive detection strategies. A humoral response to tumor antigens results in an amplified signal detected as a seropositive response based on antigen-autoantibody reactivity. Examples of such antigens include Cyclin B1, LAMR1, and p53 (1–3).

Although progress has been made in identifying an immune response to defined antigens using a multitude of technologies and some tests based on an immune response are becoming available (4, 5), several challenges need to be overcome for this strategy to be widely accepted as a means for early detection. Antigens need to be identified that are expressed at early stages. Most work done to date is based on identification of antigens expressed in tumors or tumor cells obtained at the time of diagnosis and on blood also collected at the time of diagnosis and investigated for immunoglobulin-based reactivity. The findings from these studies may not reflect the antigen-based reactivity associated with early tumor development. Different antigens may be expressed at different stages, and the balance between amount of antigen versus antibody may also be substantially altered with tumor progression. The search for antigens and the development of related biomarker tests would benefit substantially from a PROBE-based (prospective-specimen-collection, retrospective-blinded-evaluation) design in which the intended clinical application drives the design of discovery and validation studies (6). Another challenge stems from discovery of numerous antigens in independent studies, each with some evidence of seropositive response. Given that a robust test would have to include multiple antigens, in part because individuals with particular human leukocyte antigen haplotypes may generate immune responses to different antigens based on the affinity of the antigens to their human leukocyte antigen molecules, a collaborative/consortium–based approach is needed for validation that allows comparison of performance of individual antigens/markers tested on aliquots from the same cases and matched control samples as appropriate for the intended application. Such a side-by-side comparison would allow selection of the best combination of markers, which would then be subjected to another round of validation. Thus, there is a need to establish such consortia/working groups to achieve the desired objective. The choice of the specific application for an autoantibody test directed against a particular cancer type is also of critical importance, given the potential implications of a false-positive or a false-negative test result. It would be advisable at this early stage of development for such tests to identify applications that represent "low-hanging fruit," such as distinguishing benign from malignant lesions detected through

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an imaging modality. The potential for harnessing an immune response to detect precursor lesions would allow interventional strategies to prevent further progression. One such intervention is through administration of vaccines that target antigens expressed in preneoplastic cells to prevent their further progression (7).

Most of the studies dealing with autoimmunity to tumor antigens have been published in immunology and related specialty journals. Given the relevance of this field to cancer prevention and the development of biomarkers for early diagnosis, *CEBP* would represent an appropriate conduit for studies in this field. A renewed and vigorous collaborative effort to harness the immune response to tumor antigens would pay dividends.

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