Personalized medicine for cancer therapy
Lessons learned from tumor-associated antigens

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Antibody signatures may become sophisticated screening tools for early diagnosis and the development of personalized anticancer treatments. We used biopanning to enrich the immune response of head and neck squamous cell carcinoma (HNSCC) patients. This method revealed a HNSCC-specific antibody signature and allowed for the discovery of a novel oncogene, *L23*.

Head and neck squamous cell carcinoma (HNSCC) is among the ten most common cancers worldwide. Nearly half of current 600,000 HNSCC patients will succumb to the disease within 5 years of diagnosis.[1] If HNSCC is detected early, the prognosis is relatively favorable. However, due to late detection, most patients are at risk for recurrence and metastasis, which heavily contribute to mortality.[1] Hence, to improve patient survival, robust screening tests are necessary to discover HNSCC at an early stage. Moreover, a biomarker-based approach may assist in the management of HNSCC, hence improving disease outcomes.[2]

Tumor-associated antigens include proteins that are specifically expressed by malignant cells and recognized by the host immune system.[3] In this context, anticancer immune responses can be characterized to identify cancer-specific antigenic signatures.[4] Novel cancer-specific antibody signatures can therefore be used as a screening tool for early detection, allowing for the clinical implementation of effective therapeutic regimens. Moreover, as even cancers of the same type are heterogeneous diseases, difference in the response to treatment, for instance chemosensitivity or chemoresistance, are presumably linked to specific tumor-associated antigen repertoires. Only when exhaustive information about the tumor, as provided by its antigenic signature, is available, the most appropriate treatment approach can be selected.

We have recently explored anti-HNSCC immune responses to identify a novel HNSCC-specific antibody signature.[5] The most important findings of this study were 3-fold. First, we used phage display and a liquid ELISA assay to develop an HNSCC-specific antibody signature. Next, using an in silico approach, we selected tumor-associated antigens for functional validation. Finally, we identified *L23* as a bona fide oncogene through multiple in vivo and in vitro tests.

Using phage display to enrich the antibody response to tumor-associated antigens, we identified previously unknown HNSCC-associated antigens. In this setting, bacteriophage vectors that display tumor-associated antigens are used as bait, allowing for the enrichment of HNSCC-specific antibodies via biopanning. An immunomic array was thus constructed from enriched phages and used to screen additional sera from HNSCC patients and control individuals. The clones displaying the highest specificity for HNSCC were validated by the Luminex 200™ system. Ultimately, we identified a HNSCC-specific signature including multiple in-frame proteins, one of which was *L23*. Finally, using various in vitro and in vivo assays, we validated *L23* as an oncogene. An important aspect of the recent study was the use of phage libraries from tumors at different sites to detect a HNSCC-specific signature.

The potential of personalized medicine will be harnessed when efficient and reliable methods for the early detection of tumors and the choice among various treatment modalities are developed. The routine screening of sera for the presence of cancer-associated antibody signatures would facilitate early detection. **Figure 1** shows an overview of a screening and personalized treatment strategy based on a circulating antibody signature. In the proposed strategy, a "master immunomic array" would include antigens that are associated to different cancers. This would allow for the detection of a cancer-specific antibody signature using serum collected during routine physical examination. Thus, circulating tumor-specific antibodies will assist in the early detection of malignant lesions similar to prostate-specific antigen (PSA), which has promoted the early diagnosis of prostate cancer.[6]

Cancer-associated antibody signatures may also help in the choice of the most appropriate treatment modality and predict disease progression. For example, an autoantibody signature associated to
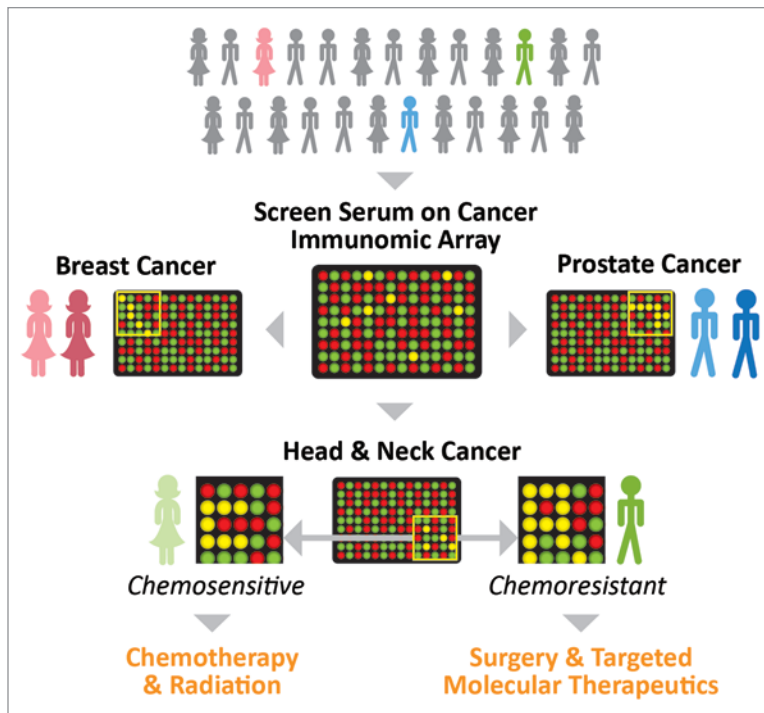
Figure 1. An immunomics approach for the early detection and personalized treatment of cancer. Serum is collected from asymptomatic individuals and screened using a cancer immunomic array. Individuals affected by different tumors are identified at an early disease stage via positive serum tests. In addition, within each cancer-specific signature, chemosensitive and chemoresistant sub-signatures may be identified by the array. These signatures would inform healthcare providers of the specific treatment needed by each patient, allowing for the development of fully personalized therapeutic regimens.

prostate cancer apparently represents a more specific screening tool than PSA levels, and may hence assist in guiding the clinical management of the disease.[7,8]

Finally, tumor-associated antibody signatures will assist the identification of novel proteins involved in oncogenesis and tumor progression and the prediction of which early stage lesions—even when treated appropriately—will progress in an aggressive manner. The identification of such aggressive tumors would allow for the choice of appropriate treatment strategies even at early disease stage. In our recent study, we validated the oncogenic role of *L23* in HNSCC. The roles that other HNSCC-specific proteins play in oncogenesis and tumor progression remain unknown. As we strive to apply the principles of personalized medicine to cancer therapy, it is exciting to consider that some tumor-associated antigens may constitute novel therapeutic targets. Perhaps through ever more performing screening tools and novel therapeutic approaches based on HNSCC-associated antigens, we will witness an improvement in the survival of patients affected by this devastating disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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