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Reports of human clinical trials aiming at antigen-specific induction of T cell and antibody responses against non–small cell lung cancers (NSCLC) have started to surface within the last 5 years (1–11). In a large proportion of trials, the nature of the antigen(s) has not been precisely determined, as in the case of vaccines with tumor cells or cell extracts and granulocyte macrophage colony-stimulating factors or dendritic cells as adjuvant, making the evaluation of successful immunogenicity difficult to measure. Immunotherapy studies where clinical efficacy is a primary end point have yet to be published in NSCLC, because by design, early phase vaccines focus solely on safety and on assessing the induction of immunity. Nevertheless, many have asked whether immunotherapy is showing enough promise and whether there is still a need to pursue the identification of antigenic targets?

The search for specificity of immune reactions to a broad number of tumors was answered with the discovery of cancer/testis (CT) antigens (12–14). It was recently reported that 10% of genes on the X chromosome are predicted to code for CT antigens (15), and expression of this overrepresented category is only detected in germ cells and placenta, but not in normal somatic tissues. In contrast, tumor tissues have a high incidence of CT antigen expression, notably NSCLCs where CT antigens are found in up to 60% of cases (16), making them prominent targets for specific tumor targeting. Of these, MAGE-3 is one of the most commonly expressed (13), but others like, NY-ESO-1, offer the additional advantage of inducing a frequent and spontaneous antibody, CD4, and CD8 T cell responses in a proportion of patients (17), often as a result of tumor growth.

In this issue, Nakagawa et al. report a survey of the expression of XAGE-1 transcript variants in 49 NSCLC specimens, and they characterize XAGE-1b as a typical CT antigen with the capacity to elicit antibody responses. Expression of XAGE-1b was found in nearly half of 31 analyzed adenocarcinomas of the lung, as determined both by RT-PCR and immunohistochemistry. This expands on previous data that have also found XAGE tumor expression in other patient populations (18–21), minimizing the risk of bias related to a specific etiology. Nakagawa et al. also report on humoral responses to XAGE-1b, assayed by ELISA and Western blot, in 5 out of 56 lung adenocarcinoma patients, but not in 40 healthy donors or 18 other NSCLC types, and antibody responses were expected to be dependent on the presence of antigen in the tumor as is the case for NY-ESO-1. Even though XAGE-specific T cell responses still remain to be defined, the detailed characterization of an antigen with frequent spontaneous in vivo immunogenicity is good news.

Implications stemming from studying the distribution and immunogenicity of more NSCLC antigens are multiple. Studies have suggested that CT expression in NSCLC may be associated with negative prognosis (22). Further analysis with more comprehensive antigen panels may reveal patterns of disease type and point out categories of patients that would benefit from particular therapies. It is still to be established whether subgroups of patients with spontaneous immunogenicity to tumor antigens may have a more favorable outcome. For this, increasing the scope of humoral responses to tumor antigens helps reach significant numbers of patients for statistical analyses, but may also help establish monitoring of associated CD4 and CD8 T cell responses from seropositive patients.

Newly identified antigens may also become useful in defining the response to NSCLC vaccines derived from whole tumors. Continued efforts to understand the nature and specificity of immunity achieved by tumor cell vaccines should be encouraged, such as screening of cDNA libraries with vaccine-induced antibodies in autologous settings (23).

And of course, the definition of more new antigens highlights prospects of future immunizations. Current assessment of vaccination with protein forms of CT antigens show that even in the case of the MAGE-3 antigen with poor natural immunogenicity, it is possible to induce a robust and consistent antibody response in the presence of adjuvant, which correlates with MAGE-3–specific CD4 T cell responses (6). It should be interesting to compare the nature of immune responses generated after MAGE-3 immunization compared to antigens with a higher level of spontaneous immunogenicity.

Important future directions will involve the detailed characterization of CD8 and helper CD4 T cell responses, the effectors, and just as importantly, the potential implication of regulatory T cells in the suppression of immunogenicity. Current approaches to immunotherapy increasingly focus on the understanding of the interplay between regulatory cells and tumors (24), and a lot still has to be accomplished especially in relation to tumor antigen specificity.
References


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