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EDITORIAL

Impact of aging on cancer immunity and immunotherapy

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The highest incidence of human cancers is seen in older people. Many parameters of immunity decrease in an age-associated manner. These two statements are each uncontroversial. However, whether the reason for the increased frequency of cancers in the elderly is due to alterations of the immune system in the old is much more controversial. Considering that the concept of immunosurveillance against spontaneously arising tumors is itself still controversial, this is hardly surprising. However, the efficacy of certain immunotherapy protocols in preclinical models and the much less reproducible but nonetheless occasionally highly effective therapeutic successes achieved in humans encourages the belief that the immune system could be exploited to control tumor growth. The following "Symposium-in-Writing" was inspired by the belief that either active or adoptive immunotherapy or a combination of both will one day soon be entering standard clinical practice. Given that most studies, preclinical and clinical both, have most often been conducted in younger individuals, it is imperative to consider the effect of age on outcome. Most obviously, the effect of age on T cell response to vaccination will be of great importance, and also the effect of the old host environment on the efficacy of adoptively transferred immune effectors needs consideration.

Here, we have gathered a collection of papers which review the effects of age on the host in terms of inflammatory status and immune responsiveness in the carcinogenic process. *Salvioli* et al. discuss possible reasons why centenarians are protected from cancer. This could be mediated by at least two different mechanisms: low IGF-1-mediated responses and elevated production of anti-inflammatory mediators. A well-preserved p53-mediated response able to block tumorigenesis or to decrease cancer aggressiveness is also critical for cancer protection in centenarians. On the other hand, *Caruso* et al. discuss the effect that inflammation has in promoting carcinogenesis. They conclude that only further knowledge of the regulation and function of inflammatory pathways in cancer will help to understand the mechanisms of tumor formation and progression, as well as to identify new targets for the refinement of novel treatments, such as the pharmacogenomics approach. Other papers then discuss different immunotherapy models where the age of the host and the age of the immune system have been specifically analyzed as variables affecting the outcome of the treatment. There is a plethora of preclinical and clinical studies utilizing dendritic cell-based therapies for cancer. However, there are only a handful of studies evaluating the effect of this type of therapy in the aging

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anti-tumor response. *Grolleau-Julius* et al. examine some of the variables affecting the initiation of the T cell response at the level of antigen presentation and define not only intrinsic changes to dendritic cells (DC) but also changes to the host environment as having a large impact on triggering an immune response. Critical to effectively translating this approach into treatment of cancers in older patients is the characterization of aging DC defects. Compromised function at the DC level may lend itself to correction by manipulating the costimulatory and/or cytokine environment, as described by *Ruby* and *Weinberg* in the context of OX-40 therapy. However, they show that this approach, while effective in young mice, is not successful in older animals, but that selected adjuvants or IL 12 can help overcome this detriment. In the paper by *Deisseroth* et al., the focus is on CD40L costimulation which is also decreased in T cells from old compared to young mice and where CD40L proteins modified to include only the extracellular domains are more effective in older animals. These are now also entering clinical trials in humans. *Provinciali* reviews his group's work with vaccination of mice with tumor cells transfected with factors such as IL 2, which was the first demonstration that immunotherapy protocols optimized for efficacy in young mice failed to yield similar results in older mice under the same conditions. Using murine breast cancer models, *Gravekamp* describes differences in responses of young and old animals to tumor antigen DNA vaccines indicating that old animals are less able to induce an effective antitumor immune response. *Lustgarten* reviews his group's work on attempting to overcome the immune deficit in old mice by combined therapies targeting costimulation, together with reducing immune suppression and enhancing adjuvant effects using TLR agonists. In a spontaneous tolerant breast cancer model, although combined treatments were able to cure young mice, the same treatment was ineffective in old animals.

The lesson from the studies reviewed by these eight papers, both the authors' own and the large corpus of work to which they refer in their articles, is that the inflammatory status and immune response to cancer is different in young and old individuals, and that cancer vaccines are less effective at older than at younger age, as shown in the different pre-clinical mouse models. Considering how many combinations of immunotherapeutic approaches (e.g. vaccines, TLR agonists, anti-suppressive agents, cytokines, etc.) may be required to induce effective anti-cancer immune responses in old animals, will the need for all these therapies decrease feasibility in elderly humans? Should a proactive approach to maintain immune function throughout aging, as well as approaches to maintain appropriate immunity in the face of chronic cohabitation with the tumor, be considered? Nonetheless, the studies discussed here also demonstrate that optimization of vaccines for older age is feasible and crucial, if challenging. Unfortunately, none of the cancer vaccines currently tested in clinical trials is optimized for older age. It is true that many obstacles such as tumor-induced immune suppression, genetic instability of tumors, poor immunogenicity of tumor-associated antigens and many more still need to be overcome also at young age. However, even when these obstacles are overcome in trials of younger patients, we will still face the problem of the age factor, which has essentially been ignored in clinical trials so far. Therefore, there is a strong argument for pre-clinical testing and optimizing of vaccines for old age in suitable model systems before attempting to apply them to cancer patients. Investigations specifically focused on immune status in elderly cancer patients should be given high priority in order to properly harness the immune system to combat cancer in the elderly. Despite the fact that mice are often criticized for not being comparable to humans, the NCI Mouse Models of Human Cancers Consortium (MMHCC) is now providing the scientific community with accurate reproducible models of human cancers that can be used in translational and pre-clinical studies. Such models are of great importance for developing vaccination strategies that are not only effective in younger patients but also in the ever-increasing numbers of older cancer sufferers.