Letter to the Editor

Spleen Cells from Young Donors Eradicate Large Tumors—Letter

Laszlo Radvanyi

We have read with great interest the recent study by Schreiber and colleagues (1) in the May 1, 2012 issue of Clinical Cancer Research. This article elegantly uses a naturally induced tumor (8101 tumor) containing a mutated high MHC-binding epitope (p68) from RNA helicase as a target for adoptive cell therapy with tumor sensitized T cells from young or old mice. The authors show that the transfer of antigen-sensitized young mouse spleen cells efficiently eradicated large established 8101 tumors, whereas those from aged mice (equivalent of middle aged humans) did not. They concluded that adoptive cell therapy, using T cells from middle aged or elderly individuals, would be largely ineffective and suggest approaches in which the transfer of MHC matched or partially matched young T cells can be used to solve this problem. These findings are highly relevant to the modern field of cancer immunotherapy by reemphasizing the need to shift more focus on considering age-related changes in immune function in designing our preclinical and clinical immunotherapy studies. However, the data also raise some additional perspectives on aging and adoptive cell therapy and cancer immunotherapy in general that should be considered.

First, T-cell adoptive therapy (e.g., TIL adoptive transfer for metastatic melanoma), conducted mostly on middle-aged patients using their autologous TIL, has in fact been quite successful in eradicating large established tumors in 50% or more of patients. However, a number of conditions need to be met, including the provision of exogenous cytokine (IL-2) and prior transient lymphodepletion to remove cytokine sinks and regulatory T cells (2). This suggests that the defects in older T cells and the host immune environment they come from can be overcome enough in many cases by ex vivo expansion, removal of competition, and cytokine help. Second, it is possible that these old T cells (shown to have an increased effector-memory phenotype) have an increased expression of coinhibitory molecules than their young counterparts due to their intrinsically more highly activated nature through aging. This is in line with the concept that older T cells are a product of the natural course of events during immune aging where the system becomes focused on preventing autoimmunity rather than fighting infection in old age (3, 4) and, as a consequence, naturally establishes greater brakes on all its T cells. Again, opportunities, however, are available to reverse this increased negative regulation (5). In fact, the success of agents such as anti-PD-1 and anti-CTLA-4 in the clinic may also be a reflection of the reversal of these aged-related effects in addition to tumor-derived immune suppression. In a corollary fashion, increasing costimulation through TNF-R family members, such as OX40 and 4-1BB, can be used to alleviate some of the defects in aged T cells during immunotherapy (3). Third, if aged T cells are in an intrinsically more differentiated (effector-memory) state, as found by Schreiber and colleagues (1) and others, they may be at a higher activation "set-point" and may in fact require increased stimulation or stronger signaling to push them through the threshold to induce proliferation and effector function. Thus, they may be more easily prone to anergy requiring stronger activation of MAPK signaling, for example. In this case, pharmacologic intervention with new drugs that further activate MAPK signaling in aged T cells may be a useful target in immunotherapy. Recent data on mutant BRAF (V600E) inhibitors showing paradoxical activation of wild-type BRAF-c-RAF dimers opens up this possibility (6). Fourth, it is possible that increased innate immune responses are required in the aged immune system to help boost the effect of T-cell therapy with older T cells. This would explain why total body irradiation before TIL adoptive cell therapy (that damages the gut and can release microbial products stimulating TLR signaling) has proven to be even better with durable response rates of >70% in metastatic melanoma (2), and why TLR ligands promise to be a game-changer in cancer vaccines. With these points in mind, it would be interesting to test these and other types of agents with young versus old transferred T cells in the 8101 tumor model and other scenarios to see if the defective older age phenotype can be reversed.

In summary, the results of Schreiber and colleagues (1) should stimulate us to finally stop avoiding the "skeleton in the closet": the issue of the aged immune system in our immunotherapy research. We need a conceptual shift in how we envision immunotherapy for cancer to also focus on therapies overcoming the effects of the age-related (as opposed to only tumor-related) brakes on the immune system and better characterize what these age-related brakes are in the first place and how they relate to tumor-derived factors (3, 4, 7). This has important ramifications in how we should design our animal (mouse) model experiments in tumor immunology and clinical approaches in the future. Finally, it argues for the need to develop standardized assays of "immune health" (7) that can be routinely applied to all our patients in the future to gauge the extent of these age-related effects, so we know how to intervene to boost the efficacy of cancer immunotherapy.

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