Chemokine Receptor 7, A New Player in Regulating Apoptosis of CD8+ T Cells in Cancer Patients

Giorgio Parmiani, Chiara Castelli, and Licia Rivoltini

One of the major issues of T cell–based cancer immunotherapy is the ability of growing tumors to impair the host immune system by acting at different steps of the immune response and on different immune cells. In fact, the tumor cytotoxic function of T cells can be blocked before their terminal effector differentiation stage (1) by the secretion of inhibitors, such as interleukin-10, transforming growth factor–β, indoleamine 2,3-dioxygenase (2), and nitric oxide; by inducing T-regulatory lymphocytes or myeloid suppressor cells; and by inhibiting dendritic cell function or migration, eventually modifying the whole host immune cell biology (see refs. 3, 4). How to overcome these immune deviation mechanisms remains a major challenge in cancer immunotherapy.

Different research groups have previously reported that peripheral blood T cells of cancer patients seem more prone to apoptosis than those of normal subjects (5–7). The proapoptotic molecule FasL, either expressed on the tumor cell surface (8) or released from tumor cells (9), has been hypothesized to play a role in the phenomenon. This pathway (defined as tumor counterattack), originally proposed by O’Connel et al. (9), has been further elucidated by more recent studies suggesting that microvesicle bearing FasL and released from tumor cells may be crucial in silencing peripheral blood T lymphocytes in cancer patients (10–12).

As usual, growing cancer cells exploit available physiologic mechanisms to impair the host immune system. This seems to also occur for apoptosis of T cells in cancer patients. An additional example is illustrated in this issue of Clinical Cancer Research where Whiteside’s group reports that the chemokine receptor (CCR) 7, a molecule known to contribute in guiding the movements of T cells and dendritic cells, and used as marker to distinguish functionally different subpopulations of T lymphocytes, has an entirely new role in protecting such lymphocytes from apoptosis in cancer patients (13). These investigators analyzed peripheral blood mononuclear cells of 36 head and neck squamous cell carcinoma patients and 16 normal controls and found that fewer CD8+CCR7+ T cells bound Annexin V (an indication that early apoptosis is occurring) than CD8+CCR7− T cells. This subset might contain memory effector cells (14) that may have been mobilized to attack tumor cells and that, for such a reason and independently of their ability to destroy tumor cells, need to be eliminated physiologically to stop the ongoing immune response, an aspect that the authors could not investigate.

Of note, the authors also showed that stimulation of peripheral blood mononuclear cells by the CCR7-specific ligands CCL19 and CCL21 resulted in the phosphorylation of Akt and increased Bcl-2 expression in CD8+CCR7+ T cells, suggesting that CCR7 protects effector T cells from apoptosis through the phosphatidylinositol 3-kinase/Akt pathway. A similar effect was previously reported by Sanchez-Sanchez et al. (15) but only for in vitro serum-deprived dendritic cells.

Whether this new function of the CCR7 molecule is activated in immune cells of patients with different tumor histologies and, more importantly, affects also the tiny subpopulation of tumor-specific T cells remains to be investigated. In fact, conflicting data exist on whether some of the many tumor-related immune suppressive mechanisms affect the whole T-cell population or are restricted to the antitumor T-lymphocyte pool. Given the high frequency of nonselected CD8+ T cells shown by Kim et al. (13) that undergo apoptosis in the peripheral blood of head and neck squamous cell carcinoma patients, it is clear that the antiaapoptotic protective effect of CCR7 does not distinguish between tumor-specific and nonspecific T cells although apoptosis seems to be accelerated in cancer patients.

This lack of specificity is found also in T-cell apoptosis induced by FasL or tumor necrosis factor–related apoptosis-inducing ligand–bearing microvesicles released by tumor cells, which seem to target T lymphocytes on the basis of their activation state (i.e., up-regulated Fas expression) rather than their Ag specificity (11). Such an apparent lack of selectivity can explain the authors’ observation that a clinically relevant difference (presence or absence of disease) was not associated with different expression of apoptosis markers in the CCR7+ and CCR7− T-cell subsets of their head and neck squamous cell carcinoma patients.

Unfortunately, other markers of CD8+ T cells (e.g., CD45, CD7, CD27, and CD28) that help in distinguishing naive from memory T cells were not defined, leaving doubts on the biological and clinical significance of the apoptotic rate of the studied population because memory T cells have been shown to be physiologically more resistant to apoptosis than naïve counterparts (16). More importantly, a clear distinction between central and effector memory T cells was not determined nor was the function of such cells, a factor that prevents a better assessment of their potential antitumor activity. Thus, it is unclear whether or not at least some of these T-cell effectors had already encountered head and neck squamous cell carcinoma antigens. Future work should be aimed at distinguishing whether enrichment in matured CD8+CCR7− T-effector lymphocytes reflects a potential...
strengthening and/or acceleration of an antitumor response by effector memory (CCR7⁺) T cells or a faster elimination of T cells that depletes patients from a fundamental tool to control cancer cell growth. In conclusion, the Kim et al. observation, although adding a new molecule to be considered as apoptotic inhibitor in peripheral blood mononuclear cells of cancer patients, does not define the importance of the lack of T-cell CCR7 on the outcome of the disease compared with the other potential mechanisms of tumor escape and immune dysfunction that may affect cancer patients.

It is clear that the authors are well aware of these limitations and, as pointed out in the discussion of their article, are making efforts for better defining the general significance and the potential clinical effect of their interesting findings.

References

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