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Rejuvenated T cells attack old tumors

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Abbreviations: ACT, adoptive cell transfer; GSK-3β, glycogen synthase kinase 3β; IFNγ, interferon γ; IL, interleukin; PD1, programmed death 1; T_{CM}, central memory T; TCR, T-cell receptor; T_{EM}, effector memory T; T_{TE}, terminally differentiated effector T; T_{SCM}, stem-cell memory T

The adoptive transfer of tumor-specific lymphocytes is actively being tested in the clinic for the treatment of chronic viral infections and some types of cancer.[1,2] In the latter setting, autologous lymphocytes are isolated from the peripheral blood or directly from neoplastic lesions, expanded to considerable amounts and optionally activated ex vivo, and eventually reinfused into the patient. To support the expansion and differentiation of adoptively transferred cells, reinfusion is often preceded by lymphodepleting treatments such as total body irradiation and/or high-dose chemotherapy and accompanied by massive doses of interleukin (IL)-2.[1,3] Antitumor T cells are functionally competent ex vivo,[4] and may induce tumor regression in vivo[5] but generally fail to persist for long periods upon adoptive transfer,[6] thus providing limited clinical benefits.

The memory T-cell compartment is organized in dozens of cell subsets, which can be identified by the analysis of distinct phenotypic and functional markers by polychromatic flow cytometry.[7] While progressively differentiating from a stem-cell memory T (T_{SCM}) stage to a central memory (T_{CM}), effector memory (T_{EM}) and terminally differentiated effector (T_{TE}) stage, T cells gradually lose or acquire specific functions in a continuum pattern.[5] In this setting, T_{SCM} cells, which have recently been shown to constitute the most undifferentiated human T-cell compartment exhibiting bona fide memory functions, are capable of generating all memory cell subsets, display superior persistence and expansion capabilities upon adoptive transfer into immunodeficient hosts and preferentially survive for long periods following the loss of the cognate antigen.[8,9]

Accumulating preclinical and clinical evidence support the notion that early-differentiated T-cell populations, such as T_{SCM} and T_{CM} cells, exert superior antitumor activities in vivo upon adoptive transfer.[5] Unfortunately, the tumor antigen-specific memory T cells that are employed in adoptive cell transfer (ACT)-based clinical trials are often highly differentiated, as they have been exposed to chronic inflammation and continuous antigenic stimulation in vivo prior to isolation. In addition, the procedures that are used for the expansion of T cells ex vivo are associated with (at least some degree of) terminal differentiation, loss of proliferative capacity and exhaustion and/or senescence.[5,10] Therefore, approaches based on early-differentiated T cells or involving a step of "rejuvenation" of exhausted T cells may considerably improve the therapeutic potential of ACT.

Inhibition of the glycogen synthase kinase 3β (GSK-3β) signaling pathway by the small molecule TWS119 has recently been shown to arrest T-cell differentiation and to stimulate the generation of T_{SCM} cells.[9] Along similar lines, Cieri et al. have recently described a clinical grade protocol to produce large numbers of T_{SCM} cells from naïve precursors by activating them with anti-CD3/anti-CD28 antibody-coated beads in the presence of IL-7 and IL-15.[11] T cells expanded by this method not only displayed a phenotype and gene expression profile similar to those of naturally-occurring T_{SCM} cells, but also could readily be transduced by a lentiviral vector coding for a tumor-specific T-cell receptor (TCR). As naïve T cells are generally abundant in the peripheral blood and can be rapidly isolated by magnetic beads or cell sorters, this technique allows for the generation of large numbers of tumor-specific T_{SCM} cells with improved effector potential.

More recently, Nishimura et al. and Vizcardo et al. have explored the use of the induced pluripotent stem cell (iPSC) technology to "rejuvenate" antigen-specific T cells.[12,13] Both groups obtained iPSCs from T-cell clones specific for the melanoma-associated antigen MART-1 or the HIV-1 protein Nef,[14] and re-differentiated them into mature, rejuvenated T cells by using T cell-specific signals. Such rejuvenated T cells maintained the original rearrangement of TCR-coding genes, produced interferon γ (IFNγ) in response to antigenic stimulation, displayed elongated telomeres (which indicate an increased replicative potential) and were capable of expanding to considerable extents in vitro. Nishimura et al. demonstrated that rejuvenated cells express much higher levels of cytotoxic molecules than the clones

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they derive from, and lack the exhaustion marker programmed death 1 (PD-1).[12,15,16] Interestingly, the phenotype of these cells does not match that of early-differentiated memory cells, but rather that of T_{EM} cells, at least relative to CD45RA and CCR7 expression.[12] In addition, rejuvenated cells appear to express only marginal levels of the co-stimulatory molecules CD27 and CD28.[12,17] It is therefore tempting to speculate, yet remains to be formally demonstrated, that the rejuvenating program allows T cells to acquire killer functions while maintaining their proliferative potential, as generally occurs during progressive differentiation. In the future, it will be important to test whether rejuvenated T cells are able to expand in vivo upon adoptive transfer into immunodeficient mice, and whether they are able to exert antitumor effector functions in xenogenic models.

As it stands, the iPSC technology combined with expansion protocols involving TWS119 or IL-7 plus IL-15 constitutes an efficient approach to generate a consistent amount of T_{SCM} cells with improved functional capacity. Further studies are needed to elucidate the true clinical potential of rejuvenated T cells. This said, the discovery of early-differentiated cells as well as the development of re-differentiation protocols constitute important tools to ameliorate the persistence and efficacy of adoptively transferred T cell for the therapy of chronic viral infections and cancer.

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