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The immune System in Health and Disease

Theme: Tumor Immunology

Harnessing Adaptive Natural Killer Cells in Cancer Therapy

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We have recently completed a Phase I/II clinical trial with transfer of haploidentical NK cells to patients with high-risk myelodysplastic syndrome. Six of the 16 treated patients achieved morphological complete remission and five of these underwent allogeneic stem cell transplantation resulting in long-term survival in four patients. The quality and number of infused NK cells as well as their transient engraftment in the recipient correlated with decrease in mutational burden and clinical outcomes. These results suggest that adoptive transfer of allogeneic NK cells may hold utility as a bridge to transplant in patients who are refractory to induction therapy. Current efforts to selectively expand metabolically optimized adaptive NK cells for the next generation NK cell cancer immunotherapy will be discussed.

Antibodies as tools in cancer immunotherapy

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Monoclonal antibody-based drugs have revolutionized current medicine and have become a major class of therapeutic agents providing effective treatment options for various human diseases, including cancer. To date, more than 25 monoclonal anti-cancer antibodies have been approved by the major regulatory agencies for clinical use. The selectivity and specificity, the unique pharmacokinetics, and the ability to engage and activate the host immune system differentiate these agents from other drugs. The development of therapeutic antibodies requires a deep understanding of disease biology, protein-engineering techniques, mechanisms of action and resistance, and the interplay between the immune system and disease cells. This talk outlines the fundamental strategies that are required to develop antibody therapies, extending from preclinical studies to human trials.

Cellular senescence: when multitasking can be dangerous

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Cellular senescence is a complex stress response whereby cells lose irreversibly their capacity to proliferate. Senescent cells develop the senescence-associated secretory phenotype (SASP), characterized by the expression and secretion of inflammatory cytokines, chemokines, growth factors and proteases. Despite a main role for cellular senescence to act as a tumor suppressive mechanism, mounting evidence indicates that senescent cells participate in multiple physiological and pathological stages, including aging and tissue repair. To more critically determine the diverse functions of senescent cells *in vivo*, we created a mouse model (p16-3MR) in which senescent cells can be detected and inducibly eliminated using the pro-drug ganciclovir (GCV).
Senescent cells induced by genotoxic drugs persist for several weeks in mouse tissues and promote local and systemic inflammation. The removal of chronic senescent cells ameliorates healthspan, and delay cancer progression in a mouse model of breast cancer.
However, transiently-induced senescent cells contribute to optimal wound healing through the secretion of the mitogenic and differentiation factor PDGF-AA.
Together, our data suggest that cellular senescence can contribute to beneficial and deleterious effects through cell-non-autonomous effects, and that this fine balance needs to be taken into account for the generation of therapies aimed at interfering with the phenotype of senescent cells.

The three main stumbling blocks for anti-cancer T-cells

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Optimal immune defense against viruses and intracellular bacteria is provided by type I immune responses, driven by cytotoxic CD8 T-cells and CD4 T-helper-1 (Th1) cells. These same cells are also the principal weapons for immunity against cancer. However, evolution has shaped type I immune responses to act optimally against acute infections, rather than tumors. It is, therefore, not surprising that CD8 and CD4 Th1-cells (so-called “anti-tumor T-cells”) often fail to control and eliminate cancer. Three stumbling blocks account for the shortcomings of anti-tumor T-cells. First, the repertoire of tumor antigens and tumor antigen-specific T-cells is often small. Second, the activation of T-cells is weak, such that anti-tumor T-cells are often unable to win the race against invading metastatic cancers. And third, the tumor microenvironment harbors multiple immune inhibitory mechanisms, rendering T-cells dysfunctional. Recent progress in cancer immunotherapy emphasizes the importance of understanding the mechanisms that regulate immune responses in tumors. Dysfunction of anti-tumor T-cells is commonly observed in cancer patients, in part caused by tumor cell-autonomous properties acquired by genetic modification, but also frequently due to natural adaptive mechanisms of T-cell inhibition. The dysfunctional state of T-cells has been termed ‘exhaustion’, based on similarities to dysfunctional T-cells in chronic infections. However, besides shared properties, recent studies have identified marked differences to infectious diseases, highlighting promising targets for novel therapies against cancer.

Anti-regulatory T cells - An alternative approach to target immunosuppressive mechanisms

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Circulating T cells that specifically target normal, self-proteins expressed by regulatory immune cells were first described in patients with cancer, but can also be detected in healthy individuals. The adaptive immune system is distinguished for its ability to differentiate between *self-antigens* and *foreign antigens*. Thus, it was remarkable to discover T cells that apparently lacked tolerance to important self-proteins, e.g. IDO, PD-L1 and FoxP3, expressed in regulatory immune cells. We recently described that these naturally-occurring specific T cells recognize both regulatory immune cells as well as malignant cells. The ability of self-reactive T cells to react to and eliminate regulatory immune cells can influence general immune reactions. Thus, utilization of e.g. IDO- or PD-L1-derived T-cell epitopes may represent an attractive vaccination strategy for targeting cancer cells and for boosting the clinical effects of additional anti-cancer immunotherapy. It was recently suggested to term these T cells anti-regulatory T cells (anti-Tregs). Pro-inflammatory anti-Tregs that react to regulatory immune cells may enhance local inflammation and inhibit local immune suppression. Anti-Tregs provide the immune system with yet another level of immune regulation and contradict the notion that immune cells involved in the adjustment of immune responses only act as suppressor cells.