Editorial

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T-cell Based Immunotherapy for Melanoma and Understanding How TLR/IL-1 Receptor-Associated Kinase (IRAK) Signal Pathway in Cancer Contributes to Cancer Progression and Chemotherapy Resistance

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Editorial

Melanoma is the deadliest skin cancer, and is notorious for its resistance to chemotherapy and radiotherapy. Dr. Geng has been using genetically engineered T cells to express tumour-reactive T cell receptors (TCR) as an immunotherapeutic approach for treating melanoma. However, a challenge for the efficacy of T-cell-based immunotherapy is that cancer cells express subdominant tumour antigens (TAgs). Dr. Geng's research indicated that stimulating Toll-like receptors (TLRs) directly on tumor reactive T cells reduces the activation threshold to poorly immunogenic TAgs. TLR2-stimulated CD8 T cells derived from T-cell receptor transgenic pmel mice responded to suboptimal levels of weakly immunogenic TAgs. Pmel CD8 T cells treated with TLR2 ligand displayed significantly increased proliferation, cytokine production, and cytolytic activity. Treatment with pmel T cells plus purified TLR2 ligand showed increased antitumor activity in mice against an established melanoma tumor. Also, TLR2 stimulation on CD8 T cells from melanoma patients decreased the activation threshold to TAgs and resulted in augmented production of various effector molecules and cytolytic activity [1].

However, TLR ligands have the limited efficacy in cancer therapy due to the very short half- life *in vivo*. Therefore, Dr. Geng genetically engineered human T cells to express the MART-1 TCR, a T-cell receptor that recognizes the melanoma antigen MART-127-35, and to deliver the TLR5 ligand flagellin to tumor sites. Engineered T cells expressing the TCR along with flagellin showed greater proliferation, increased cytokine production and cytolytic activity against melanoma cells. In a xenogenetic mouse model of melanoma, mice treated with engineered human T cells showed tumor regression and prolonged survival [2]. Dr. Geng concludes that tumor-reactive T-cells capable of secreting TLR5 ligand generate potent and long-lived antitumor activity by: (1) delivering a TLR agonist directly to the tumor site, (2) co-stimulating T-cell responses (cytokines, expansion, and cytolytic activity), (3) inducing the production of chemokines by melanoma cells, (4) recruiting other immune cells to the tumor site, (5) reducing CD11 (+) Gr1 (+) myeloid-derived suppressor cells.

TLRs are not only expressed by immune cells but also by various tumours including melanoma, however it is still unclear whether they play a role in cancer cells. Dr. Geng and his colleagues firstly investigated the protein expression levels of TLRs and TLR-related proteins including the TLR/IL-1 receptor-associated kinases (IRAK) in melanoma cell lines and melanoma tumor biopsies. The results showed that among them, highly activated phospho-IRAK-1 and phospho-IRAK-4 were expressed in the absence of TLR stimulation. Inhibiting IRAK-1,-4 signalling in melanoma cells with the pharmacologic inhibitor induced apoptosis *in vitro* in combination with a chemotherapy drug vinblastine. In a xenograft model, the combined pharmacologic treatment delayed tumor growth in mice bearing an established melanoma and prolonged mouse survival [3]. Dr. Geng proposes IRAK-4 as a novel promising cancer therapeutic target to enhance chemotherapy. Dr. Geng's current research work will significantly reduce mortality and improve the quality of life for patients suffering from cancer.

Reference

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