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Commentary

Impact of PFT-α Treatment on CAR T Cell Engineering and Function

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DESCRIPTION

Chimeric Antigen Receptor (CAR) T cell therapy has emerged as one of the most potential strategies in cancer immunotherapy, demonstrating remarkable success in treating hematologic malignancies. However, the effectiveness of CAR T cell therapy can be limited by factors such as T cell exhaustion, apoptosis and impaired proliferation. Recent studies have described the role of pharmacological agents in enhancing CAR T cell function and persistence and Pifithrin-α (PFT-α), a small molecule inhibitor of p53, has achieved significant attention in this context. PFT-α is known for its ability to modulate the p53 tumor suppressor pathway, which plays a central role in regulating cell apoptosis, proliferation and response to cellular stress. This article examines the impact of PFT-α treatment on CAR T cell engineering and its subsequent effect on T cell functionality.

The p53 pathway is important for maintaining genomic stability and regulating cell cycle progression. However, in the context of CAR T cell therapy, p53 activation can lead to unintended consequences, such as increased apoptosis and reduced T cell persistence. PFT-α inhibits p53-mediated apoptosis, thereby potentially enhancing the survival and expansion of CAR T cells during *ex vivo* expansion and after their infusion into patients. This pharmacological intervention allows CAR T cells to withstand the stress associated with genetic engineering, activation and large-scale proliferation, leading to improved functional persistence and therapeutic outcomes.

During the engineering phase, T cells are subjected to viral transduction, cytokine stimulation and repeated cell divisions, all of which can induce cellular stress and p53 activation. Excessive activation of p53 in this phase can trigger apoptotic pathways, reducing the yield of functional CAR T cells. PFT-α treatment has been shown to counteract this stress-induced apoptosis, promoting a higher survival rate of CAR T cells during manufacturing. This effect is particularly beneficial for therapies requiring large numbers of T cells, as it ensures a strong and viable cell product for infusion.

Moreover, PFT-α has been reported to enhance the metabolic fitness of CAR T cells. Metabolic reprogramming is essential for maintaining CAR T cell functionality, especially in the harsh tumor microenvironment, where competition for nutrients and oxygen is intense. PFT-α-treated CAR T cells exhibit improved mitochondrial function, reduced oxidative stress and enhanced glycolytic capacity, all of which contribute to prolonged survival and sustained antitumor activity. These metabolic advantages enable CAR T cells to maintain their effector functions even in nutrient-deprived conditions within solid tumors.

Another significant aspect of PFT-α treatment is its impact on T cell exhaustion, a common challenge in CAR T cell therapy. Repeated antigen exposure and persistent stimulation often lead to T cell exhaustion, characterized by the loss of effector functions and upregulation of inhibitory receptors such as PD-1, TIM-3 and LAG-3. Studies suggest that PFT-α can alleviate T cell exhaustion by preventing p53-induced apoptotic signals and reducing the expression of exhaustion markers. This not only enhances the cytotoxic activity of CAR T cells but also prolongs their functional persistence *in vivo*.

While the preclinical evidence supporting the use of PFT-α in CAR T cell therapy is compelling, there are still challenges and limitations that need to be addressed. For instance, prolonged inhibition of p53 may carry risks such as genomic instability or impaired tumor surveillance by endogenous immune cells. Therefore, optimizing the timing, dosage and duration of PFT-α treatment is critical to minimize potential side effects while maximizing therapeutic benefits.

PFT-α treatment represents a potential strategy to enhance CAR T cell engineering and functionality. By inhibiting p53-mediated apoptosis, improving metabolic fitness and alleviating T cell exhaustion, PFT-α can potentially overcome several limitations associated with current CAR T cell therapies. However, further clinical studies are needed to validate these findings and ensure the safety and efficacy of PFT-α as an adjunct therapy in CAR T cell treatment protocols.

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