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Deubiquitinase as Potential Targets for Cancer Immunotherapy

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Introduction

During the last few decades, immunotherapy is considered to be an important approach to help our immune system to fight various kinds of diseases, such as tumor [1,2]. Sometimes, it works very well for some types of cancers, for example: bladder cancer [3], colorectal cancer [4], breast cancer [5,6] and lymphoma [7]. Especially, when patients fail of traditional radiation and chemotherapy treatment. Several kinds of immunotherapy strategies are being applied to treat cancer, including monoclonal antibodies; immune checkpoint inhibitors; cancer vaccines and non-specific immunotherapies. Deubiquitinase (DUB) have been well recognized as important regulators for innate and adaptive immune responses and as potential therapeutic targets for the treatment of cancer diseases [8,9]. Moreover, several small molecules specific targeted on DUBs have been discovered and developed for the treatment of various types of cancer [10].

Regulation of Innate Immune Response by DUBs

Dendritic cells, a major type of innate immune cells involved in the regulation of T cell activation, inflammation, as well as tumor microenvironment [11], is considered to be a potent mediator bridging the innate and adaptive immune systems [12,13]. It could uptake and present the tumour-specific antigens to activate $CD4^+$ or $CD8^+$ T cell response [14]. Recent studies reported an unexpected role for a deubiquitinase, Trabid, in regulating TLR signaling in dendritic cells, driving inflammatory T cell responses and demonstrated, for the first time, an epigenetic mechanism that mediates NF-κB activation and induction of the IL12 and IL23 proinflammatory cytokine genes by TLRs. This mechanism involves Trabid-mediated deubiquitination and stabilization of the demethylase Jmjd2d, which in turn "erases" repressive histone methylation marks at IL12and IL23 promoters [15]. Furthermore, another deubiquitinase, Mysm1, could regulate the steady-state DC development via epigenetically regulate Flt3 promoter region [16]. Moreover, deubiquitinase A20 acted on the regulation of DC maturation and activation, then maintained these cells in tolerance status. Depletion of A20 in dendritic cells could increase their antigen presentation ability and promote Th1 and Th17 differentiation [17].

Regulation of T cell Activation by DUBs

Activation of antigen-specific T cell response is critical for the treatment of cancer and viral diseases [18-21]. The activated antigen specific effector T cells could migrate into inflammation or tumor deposits through lymph node [22]. Therefore, modulation of immune response could benefit the treatment of cancer immunotherapy [23]. Ubiquitination, as the pivotal posttranslational modification, is an important player in the regulation of T cell development, homeostasis and activation [24,25]. Recently, Otud7b, an OUT family of DUB, was identified as pivotal regulator of TCR proximal signaling [26]. In addition, depletion of Otud7b impaired the activation of TCR downstream signaling factors Zap70 and refractory to T cell-mediated autoimmunity and inflammation. Moreover, DUBs also could modulate T cell activation through an indirect regulation of the regulatory T cells (Tregs). Recent studies demonstrated that USP7, a deubiquitinating enzyme, could enhance the stability and function of Tregs. Interestingly, pharmacological inhibition or knockdown of USP7 impaired their inhibitory function along with T cell activation [27].

DUBs Inhibitors on Cancer Immunotherapy

The FDA approved Velcade (bortezomib), a 26S proteasome inhibitor, to be used for the treatment of hematologic and solid-organ malignancies, which indicating the potential roles of Ubiquitin proteasome system in fighting tumor [28]. In addition, another proteasome inhibitor Kyprolis (carfilzomib), was approved for the treatment of multiple myeloma in 2012 [29]. Unfortunately, some patients showed resistant or develop resistance during the treatment with these inhibitors. Also, due to the non-specific target of these inhibitors result in high toxic effects.

In the meantime, more specific inhibitors targeting upstream molecules of the ubiquitin proteasome system become more promising and have been investigated as potential targets for tumor therapy [30-32].

Inhibition of single or multiple DUBs by synthetic small molecule inhibitors has attracted pharmacological companies and research institutes' interest. Inhibition of USP14 leads to increased degradation of oxidized proteins and benefit to reduce aberrant proteins under stress condition [33]. Thus, the DUBs inhibitor IU1 showed potential promising effects on the therapeutic benefits of Alzheimer's disease. With high throughput screening approaches, Dr. Chen and his colleagues identified selective small molecule inhibitors (Pimozide and GW7647) targeting at human USP1/UAF1. They also demonstrated that these inhibitors could synergize with traditional drug cisplatin in the treatment of non-small cell lung cancer cells [34].

USP7 plays critical roles in the regulation of cell cycle along with tumor suppressors and oncogenes. Therefore, it has great possibility as a novel therapeutic target for cancer therapy. Reverdy et al. identified selective small molecule inhibitors against USP7 through biochemical assay and activity-based protein profiling in living systems and reported that cell proliferation and cell cycle was altered by the treatment of USP7 inhibitors, which indicated that USP7 is a promising therapeutic target for cancer therapy [35].

Conclusion

Deubiquitinase plays pivotal roles in the regulation of immune response along with cell proliferation and cell cycle, which draws increased attention to be used as novel strategies for cancer patients. Translational studies using pharmacological DUBs inhibitors suggest that targeting DUBs to modulate immune response along with directly induce its apoptosis, will lead to promising therapeutic opportunities in clinical application.

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