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CORRESPONDENCE

Tumor immunity: a novel dimension for PROTACs to conquer cancer?

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Nowadays, tumor immunotherapies have achieved unprecedented therapeutic effects in the treatment of cancer [1]. Accumulating evidences indicate that tumor immunotherapies intrinsically depend on the specific triggering of T cells by neoantigens, and the quantity and quality of neoantigens are likely to be the core factors affecting the immunotherapeutic effect of cancers [2]. Neoantigens are essentially MHC-I presented short peptides, which are mainly arised from proteasome-degraded mutant proteins. Although a large number of somatic mutations existed in tumor cells, neoantigens are still scarce. Notably, the generation of neoantigens can be regulated. Lu et al. [3] found that enriching neoantigens of cancers by regulating the mRNA splicing process can trigger anti-tumor T cell response or enhance checkpoint immunotherapy to inhibit tumor growth. This discovery indicated that effective positive regulation of tumor immunotherapies can be achieved by increasing the abundance of neoantigens. However, this strategy lacks tumor specificity. Additionally, Fidanza et al. [4] regulated the degradation process of the vaccine in proteasome by designing a single tyrosine substitution (Y6 PepVIII) to strengthen the cellular anti-tumor immune response and increase the survival rate of mice, which implies that regulating the degradation of mutant proteins may be another effective way to enrich tumor neoantigens.

As a matter of fact, there are many significant proteins associated with cancer that are difficult to be degraded, such as Kirsten Ras Sarcoma Protein (KRAS), which may be one of the important factors affecting the abundance of neoantigens and even leading to the failure of neoantigen generation [5]. Nonetheless, these refractory proteins can be easily degraded by proteasome with the help of proteolysis-targeting chimeras (PROTACs). For example, in virtue of a VHL-recruiting PROTAC, $KRAS^{G12C}$ is successfully degraded [6]. PROTACs are heterobifunctional molecules consisting of two different ligands, which are responsible for binding to a protein of interest (POI) and an E3 ligase, respectively. It induces the ubiquitination of the POI by bringing it to close proximity to the E3 ligase, then POI is efficiently degraded by proteasome [7]. Up to now, there are more than 50 proteins have been successfully degraded by various PROTACs. To our excitement, PROTACs may be ideal candidates to enrich the neoantigens of tumors by specifically improving the degradation of mutant proteins (Fig. 1).

Interestingly, there have been some studies verifying the possibility and correctness of the conjecture. One research utilized a PROTAC named Datg-7 to induce the degradation of fusion protein including FKBP12F36V and OVA peptide by the proteasome, therefore increasing the OVA peptide presentation on MHC-I, and they first discovered that PROTAC had a new immune-stimulating characteristic. What's more, the fact that mature or stable antigens can serve as an important source of peptides feeding the MHC-I presentation pathway was also demonstrated in this study [8]. Jensen et al. [9] also found that ARV-825 (JQ1-CRBN), ARV-771 (JQ1-VHL), and JQ1-MDM2 promoted the presentation of bromo- and extra terminal domain (BET) peptides. But it is still not apparent if the change in MHC-I peptide quantity caused by degraders is adequate to activate T cells killing tumor cells. Then another research answered this question. Massafra et al. increased the presentation of antigenic BRD4 peptides shown on MHC-I by corresponding BRD4 PROTAC. Furthermore, they also revealed that the effect of PROTAC-dependent degradation on the increase of antigens presentation is sufficient to trigger the immune response against cancer cells for the first time. To draw this conclusion, they explored the biological justification for combining a degrader and an antigen-directed immunotherapeutic for oncology purposes in a coculture model of cancer cells and T cells [10].

PROTACs have been developed for nearly 20 years and have entered the clinical trials at present, but most of the researches only focus on protein degradation. Although it has a certain inhibitory effect on tumors, it is difficult to completely eliminate tumor cells. Therefore, a more comprehensive and in-depth analysis of the mechanism of PROTACs from the perspective of tumor immunity is bound to provide a new idea for the success of PROTACs in tumor treatment. What's more, more tumor immunotherapies have gradually emerged, such as checkpoint inhibitors, tumor vaccines, CAR-T and so on. These therapeutic regimens involve a very important process in the immune process: the presentation of degraded peptides. Therefore, PROTACs will unfold a new picture in the field of immunotherapy in the near future.

While these surprising results initially verified our suppose, these researches have only observed the phenomenon. Not only the degradation efficiency but also the location of the protein hydrolysis site has a significant influence on the generation of neoantigens. Hence, the precise regulation of protein degradation efficiency and degradation mode by PROTACs is the opportunity

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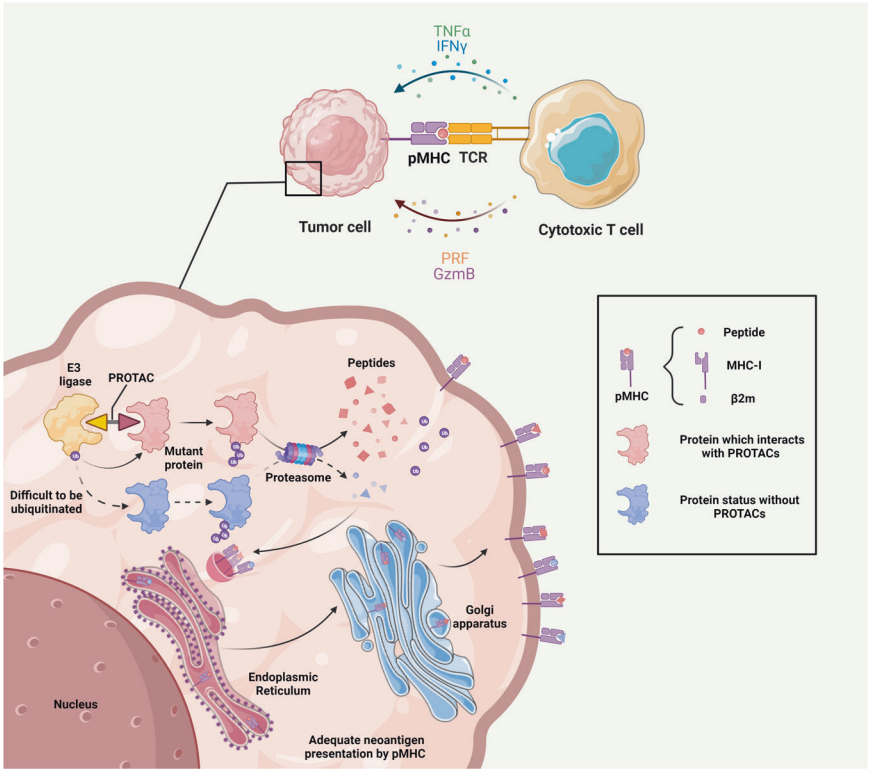

Fig. 1 PROTACs drive neoantigen presentation and T cell activation. Some muntant proteins are difficult to be degraded by ubiquitin-proteasome system, which makes them unable to be presented to generate neoantigens [5]. Fortunately, PROTACs can enrich the aboundance and types of neoantigens by promoting the degradation of mutant proteins, which may futher trigger the tumor immune effect [10].

and challenge for us to truly use PROTACs to achieve tumor immunotherapy regulation.

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ADDITIONAL INFORMATION

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