Commentary

A Translational Perspective of a Deubiquitinase Inhibitor in Antitumor Immunity

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Usp7−/− Treg cells express more IFN-γ and display a Th1-like phenotype. All these data suggest that inhibition of Usp7 might impair Treg cell function and potentially promote anti-tumor immunity. Therefore, pharmacologic blockade of Usp7 might provide therapeutic clues towards the effective immunotherapy against cancer.

Interestingly, Treg cells abrogated their suppressive activity after pre-treatment with Usp7 inhibitor (Usp7i) P5091 or its derivative P0217564, which is accompanied by dramatic loss of Tip60. These observations were consistent with previous studies that Tip60 critically regulates the function of Treg cells through promoting acetylation, dimerization and function of Foxp3. Meanwhile, Usp7i treatment promoted the ubiquitination of both Foxp3 and Tip60, and also inhibited the formation of Foxp3 dimers. However, the expression level of Foxp3 protein was comparable in WT and Usp7−/− Treg cells, which suggests the existence of a redundant role of Usp7 in stabilizing Foxp3 protein.

Therefore, pharmacologic inhibition of Usp7 impairs Treg cell function, likely through mechanisms that are Tip60-dependent rather than simply via Foxp3 ubiquitination.

The therapeutic application of Usp7i in several mouse tumor models shows promise, especially the combination of Usp7i with other anti-tumor therapies. Usp7i treatment decreased the intratumoral accumulation of Foxp3+ Treg cells and significantly inhibited tumor growth. More importantly, Usp7i treatment promoted the accumulation of IFN-γ-producing tumor-antigen specific CD8+ T cells in the tumor microenvironment, which greatly contributed to the temporal release of immune tolerance. Therefore, from a translational perspective, Usp7i-mediated Treg cell inhibition shows potential as a novel approach in the immunotherapy against tumor.

The fact that Usp7 has multiple substrates could be one of the major concerns in clinical trials of Usp7 inhibitors (Nicholson and Suresh Kumar, 2011). Another problem could be the wide expression of Usp7 in many cell types. Therefore, Usp7 inhibitors might affect other cell populations rather than simply inhibit the function of Treg cells through Tip60 in vivo. Another preclinical study showed that Usp7i directly induced apoptosis in multiple myeloma cells (Chauhan et al., 2012). However, from the proposed molecular mechanism in the current study by Wang et al., Usp7i compounds can have dominant effects on Foxp3+ Tregs over that of other immune cell types, including host effector T cells and CD8+ T cells. Therefore, pharmacologic modulation of Treg
cells using Usp7i compounds gives a new potential to break the immune tolerance in the tumor microenvironment.

In summary, the data by Wang and colleagues proposes a potential immunotherapy against tumors by targeting Usp7, which impairs Treg cell function and subsequently breaks the immune tolerance in the tumor microenvironment. Therefore, these preclinical findings suggest that Usp7 targeting immunotherapy to selectively diminish Treg cell function, as well as to directly induce tumor cell apoptosis, could have practical significance in clinical applications.

Disclosures

The authors declare no conflicts of interest.

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