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Beyond CTLA-4 and PD-1: Orphan nuclear receptor NR2F6 as T-cell signaling switch and emerging target in cancer immunotherapy

Victoria Klepsch
Medical University Innsbruck, Austria

Modulation of the immune system for the treatment of primary and metastatic tumors in cancer patients has been a goal for many decades. Very recently, blockade of immune checkpoints CTLA-4 and PD-1 has emerged as promising cancer immune therapies. Even though encouraging, there is an unmet medical need as still only a very limited number of patients respond to and are potentially cured by these therapies. In contrast to cell surface checkpoints, there are cancer therapeutic targets that are located inside the immune cells and are amenable to pharmacological modulation. Based on our published and unpublished findings that genetically *NR2F6*-deficient mice are able to immunologically reject otherwise lethal tumor burdens; we have identified and preclinically validated the orphan nuclear receptor *NR2F6* (nuclear receptor subfamily 2, group F, member 6; alias Ear2 and COUP-TFIII) as a bona fide immune checkpoint. We could show that genetic ablation of *NR2F6* significantly improves survival in the murine transgenic TRAMP prostate cancer model. Furthermore, *NR2F6*$^{-/-}$ mice spontaneously reject implanted tumors and develop host-protective immunological memory against tumor re-challenge. This is paralleled by increased frequencies of both CD4^{+} and CD8^{+} T-cells and higher expression levels of interleukin-2 and interferon-γ at the tumor site. This defines *NR2F6* as an intracellular and potentially also druggable immune checkpoint, where the presence of *NR2F6* limits effector T-cell activation within the tumor microenvironment governing the amplitude of anti-cancer immunity, representing a promising avenue for development of alternative immune checkpoint inhibition treatment regimens.

Biography

Victoria Klepsch has received her PhD degree from the Medical University Innsbruck. She is a Postdoctoral Fellow at the Medical University Innsbruck in Gottfried Baier's Lab. She has published 3 papers in well-reputed journals and has been working on *NR2F6* and tumor immunology since 4 years continuing investigating in depth in this nuclear receptor *NR2F6* in T-cell biology and cancer immunity.

victoria.klepsch@i-med.ac.at

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