RESEARCH HIGHLIGHT

Tumor microenvironment squeezes out the juice from T cells

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Escaping the immune response is a major prerequisite for tumor to emerge and progress, and many different mechanisms are in place within the tumor microenvironment (TME) to reach this aim, including the induction of CD8$^+$ T cell exhaustion. In a recent publication in *Cell*, Zhang and colleagues showed that biomechanical stress occurring in the TME enforces CD8$^+$ T cell exhaustion through the expression of the transcription factor Osr2 that acts as an epigenetic regulator.

First identified in chronic infection, exhausted CD8$^+$ T cells express multiple inhibitory receptors, have reduced effector functions, and are not able to efficiently control pathogens or tumors.[1] The main inducer of exhaustion is the continuous triggering of the T cell receptor (TCR),[2] but several factors present in the tumor microenvironment (TME) such as metabolite deprivation, high pH or hypoxia could further participate in the induction and maintenance of this program in a cancer-specific manner.[3] The exhaustion program is established through the expression of several transcription factors (TFs) such as TOX, NFAT1 and NFAT2, in a two-step process starting with precursor exhausted TCF1$^+$TIM-3$^-$PD-1$^+$CD8$^+$ T cells (so called Tpex cells) that further differentiate into terminally exhausted TCF1$^-$TIM-3$^+$PD-1$^+$CD8$^+$ T cells (so called Tex cells).[4]

Even though several immunotherapy strategies are widely used for several cancer treatments, most cancer patients relapse or remain unresponsive to treatment. A major limitation to efficient immunotherapy is the intrinsic attenuation of tumor antigen-specific T cells, which underlies the T cell exhaustion.[5] Therefore, understanding the establishment and maintenance of the CD8$^+$ T cell exhaustion program within the TME is a major contribution to the improvement and development of potential new immunotherapies.

In their recent publication in *Cell*, Zhang and colleagues investigated the impact of the mechanical stress (MS) occurring in the TME via the extracellular matrix (ECM) architecture and stiffness on the regulation of the exhaustion program in CD8$^+$ T cells (Fig. 1).[6] They showed that MS impacts the level of T cell exhaustion in vitro and in vivo in a Piezo1-dependent way. Piezo1 is a mechanosensitive ion channels that allows the transduction of mechanical stimuli by increasing Ca^{2+} influx. By using an agonist of Piezo1, the authors discovered that the TF Osr2 was specifically upregulated by MS in a Ca^{2+}-dependent manner, and was highly expressed in CD8$^+$ tumor-infiltrating lymphocytes but not after acute or chronic infection (Fig. 1).

To further characterize Osr2 activity, the authors generated a *Osr2* knockout (KO) mouse model and investigated CD8$^+$ T cell phenotype in MS conditions. Similar to the observation with the Piezo1-deficient cells, *Ors2* KO was sufficient to induce an increased IFNγ/TNFα and a decreased PD-1/TIM-3 expression which indicated that *Ors2* KO attenuated the exhaustion profile. Moreover, after tumor induction in those mice, *Ors2* KO CD8$^+$ T cells were more infiltrated in the tumor and exhibited an effector profile at the protein level with an increased effector vs exhaustion and a decreased exhaustion vs memory gene signature. This correlated with a higher Ors2 expression observed in tumor-infiltrating Tex both in mouse and human. Importantly, this induction was specific to the tumor-induced MS since Ors2 expression was absent in Tex isolated from both acute and chronic infection models. Using an Ors2 overexpression model both in vitro and in vivo in the infection settings, the authors demonstrated that Osr2 drives the downregulation of effector genes and upregulation of exhaustion genes. Moreover, they showed that Ors2 functioned as an epigenetic regulator, since it allowed the recruitment of HDAC3 (a well-known histone deacetylase that enable chromatin closing) onto the promoter of cytotoxic genes (such as *Ifng* or *Prf1*) resulting in the inhibition of their expression. Finally, since one main limitation of CAR-T cell therapy for solid cancer treatment is the establishment of exhaustion profile,[7] the authors generated CAR-T cells using T cells isolated from *Osr2* KO and wild-type mice. Here they showed that 15 days after transfer to tumor-bearing mice, the *Osr2* KO CAR-T cells were higher in numbers and exhibited a more activated and less exhausted phenotype, opening new possibilities to ameliorate CAR-T cell generation and function.

This study highlights the importance of the TME on the induction and maintenance of the CD8$^+$ T cell dysfunction. In particular, the authors describe how the MS through the Piezo1/Osr2 signaling exacerbates the T cell exhaustion within the tumor. Likewise, other studies have emphasized the role of the tumor-specific local environment in CD8$^+$ T cell dysfunction, with the recent example of NFAT5-driven exhaustion through increased osmolarity,[8] or the studies showing the important role of hypoxia in the regulation of exhaustion[9,10] (Fig. 1). Here, Zhang and colleagues put forward new challenges for immunotherapy treatment by not only focusing on the immune cells themselves but also extending to the physical and chemical tumoral environment with potential biomechanical checkpoints.

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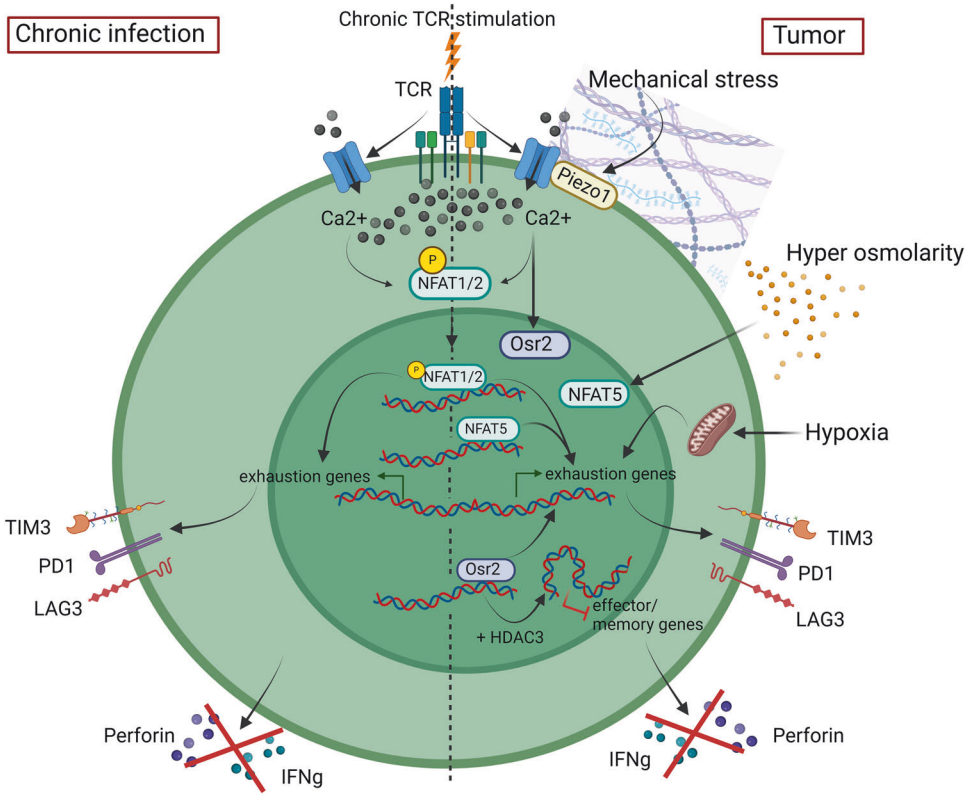

Fig. 1 Physical and chemical properties of the TME participating in T cell exhaustion. If TCR chronic triggering is a common feature between chronic infection and tumor, several physical and chemical parameters within the TME also participate in tumor-specific T cell exhaustion. Mechanical stress via the Piezo1/Osr2 axis, hyper osmolarity through NFAT5 activity or hypoxia-induced mitochondrial stress all participate in the induction and maintenance of the T cell exhaustion program with transcriptional and epigenetic rearrangements. Made with Biorender.

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ADDITIONAL INFORMATION

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