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RESEARCH HIGHLIGHT

Dendritic cells are stressed out in tumor

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A recently paper published in *Cell* reports that dendritic cells (DCs) are dysfunctional in the tumor environment. Tumor impairs DC function through induction of endoplasmic reticulum stress response and subsequent disruption of lipid metabolic homeostasis.

Tumors develop diverse strategies to escape tumor-specific immunity. Tumor-infiltrating dendritic cells (tDCs) are dysfunctional and/or mediate immune suppression [1]. Cubillos-Ruiz *et al*. [2] showed in their recent *Cell* paper that tDCs exhibit an activation of the unfolded protein response (UPR), as indicated by the presence of high levels of spliced XPB1, and this may be attributed to reactive oxygen species (ROS) in tumor, which induces lipid peroxidation, leading to the endoplasmic reticulum (ER) stress in tDCs. Furthermore, they demonstrated that UPR activation in tDCs results in poor DC function, which is accompanied by impaired lipid metabolism and subsequent reduction of T cell anti-tumor immunity. Thus, these observations present a novel mechanism for tDC malfunction.

ER stress is evoked by the presence of unfolded or chemically modified proteins. In short, the presence of damaged proteins is sensed by the proteins in the ER membrane. Of these, IRE1α can remove a short nucleotide sequence from mRNA encoding XBP1 protein. This splicing event facilitates XBP1 translation. XBP1 protein binds to consensus sequences in target genes and activates their expression [3]. Many XBP1 target genes are fatty acid synthesis enzymes. Enhanced production of fatty acids leads to the formation of lipid droplets inside the cytoplasm and extension of the ER compartment due to efficient intracellular membrane formation [3]. Therefore, this mechanism is a form of adaptation of the cell to the harsh environment, which sustains the production of functional proteins. In such a context, the article by Cuillos-Ruiz *et al*. [2] shows intriguing data on the XBP1 pathway in silencing DC function in the tumor environment.

First, Cubillos-Ruiz *et al*. [2] observed that tDCs express high levels of spliced XBP1, its direct target genes and other markers for the ER stress response. Targeted deletion of *XBP1* in $CD11c^+$ DCs reveals an association of the XBP1-dependent ER stress response with immunosuppressive properties of tDCs. DC-specific deletion of *XBP1* not only inhibits tumor growth and prolongs animal survival, but also reduces tumor peritoneal metastasis, ascites accumulation, and splenomegaly in an ovarian cancer-bearing mouse model.

Next, the authors elucidated why the XBP1 pathway in tDCs is highly activated. Unexpectedly, neither typical tumor-associated cytokines nor hypoxia can efficiently stimulate XBP1 activation. Interestingly, tDCs contain high levels of lipid peroxidation byproducts bound to the proteins, which is associated with the production of ROS. Microarray analysis revealed that DC-specific *XBP1* deletion downregulates both UPR pathway-dependent genes and lipid metabolism, which results in lower total lipid production, loss of lipid droplets in the cytoplasm and decreased production of triacylglycerides. This phenotype can be recapitulated by chemical inhibition of ROS formation or IRE1α and XBP1 signaling. Furthermore, XBP1-deficient DCs are potent stimulators of OT-1 T cells. Adoptive transfer of T cells isolated from metastatic tumor-bearing mice with DC-specific *XBP1* deletion also shows their superior ability to control tumor growth.

On the basis of these observations, the authors tested the effects of therapeutic intervention with the usage of nanocomplexes containing XBP1 siRNA. The size of lipid particles or nanocomplexes determines the anatomical location of specific drug delivery [4]. Additionally, they previously optimized the nanocomplexes for selective engulfing by DCs [5]. They found that administration of the nanoparticles containing XBP1 siRNA causes potent T cell activation, which is accompanied by reduced cancer metastatic foci and improved animal survival.

The paper by Cubillos-Ruiz *et al*. [2] provides an important insight into DC biology in general. Since the identification of Toll-like receptor (TLR) signaling, the main direction in DC biology has been associated with PAMP and DAMP recognition in various degrees (Figure 1). However, the link between cellular metabolism in specific microenvironment and DC biology is poorly explored (Figure 1). The ER stress response has previously been observed in DCs [6, 7]. It is thought that in response to ER stress, XBP1 is crucial for DC generation, survival, and function [6, 7]. The conceptual link between XBP1 signaling and DC biology is as follows [8]: (i) stimulation of DCs leads to ER stress; (ii) ER stress activates UPR/XBP1 pathway; (iii) XBP1 activates lipid synthesis genes; (iv) lipids are used

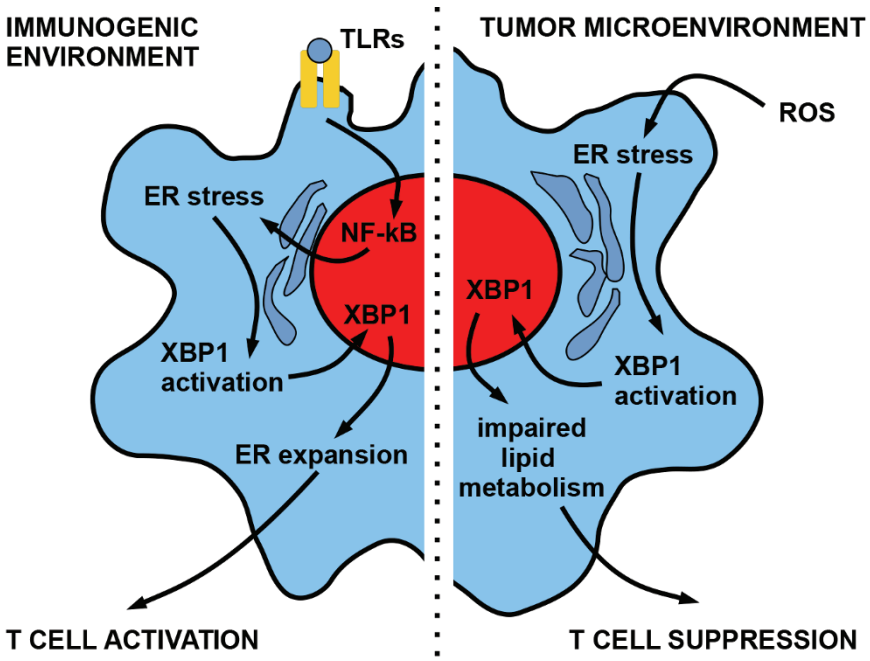

Figure 1 Double-faced role of XBP1 signaling pathway in DCs. Left: under immunostimulatory conditions, DCs receive signals from Toll-like receptors. NF-κB signaling induces a XBP1-dependent ER stress response, which enhances lipid metabolism. Formation of new membranes expands ER and Golgi compartments, which enhances cytokine production and secretion [7]. Right: In the tumor microenvironment, DCs are exposed to ROS, which also results in ER stress. However, in this case DC lipid metabolism is impaired and DCs acquire an immunosuppressive phenotype [2].

for the extension of the ER and Golgi compartment, which are of importance for cytokine production and secretion [9, 10]. Now, the authors challenged this concept in the context of cancer. The authors demonstrated that XBP1 signaling is strongly associated with poor T cell activation and limitation of XBP1 signaling leads to improved T cell function in the tumor environment (Figure 1). Thus, the paper sheds a new light on DC biology.

Of course, as with any interesting work, the article raises more questions than answers. For example, which immune-related properties of DCs are "selectively" affected by the XBP1 pathway? Is there an actual cause-and-effect relationship between aberrant lipid accumulation and the immunosuppressive phenotype of tDCs? The authors observed no obvious change in PD-L1 (B7-H1) expression in DCs, but noticed reduced surface levels of peptide-loaded MHC-I complexes in wild-type tDCs as compared to XBP-deficient tDCs. However, it remains unknown whether and how DC cross-presentation is involved in tDC function regulated by ER stress, XBP1 activation, and lipid metabolism. Human ovarian cancer-associated DCs express high levels of B7-H1 and limited IL-12 [11]. It would be interesting to thoroughly examine the cytokine profile, and the B7 and TNF family members, along with lipid pathway manipulation in *XBP1*$^{-/-}$ DCs. It is well known that ER morphology and function is substantial for the synthesis of membrane proteins and cytokines, which would be affected by the XBP1 pathway. Paradoxically, a restricted ER stress response can help immune reaction, which requires the expansion of the ER compartment. Another question is how and which lipid synthesis and metabolism pathway is targeted by XBP1 in DCs (or/and tumor cells in the same environment). Obviously, future studies are warranted to address these important questions.

In conclusion, the paper by Cubillos-Ruiz *et al*. [2] opens an interesting chapter for scientifically and therapeutically exploring DC biology in a specific metabolic environment. Given that silencing XBP1 signaling in DCs enhances tumor immunity, and XBP1 is an intrinsic pro-tumor factor, it is reasonable to assume that targeting this pathway may be beneficial in patients with cancer and could kill two birds with one stone.

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References

1 Zou W. *Nat Rev Cancer* 2005; **5**:263-274.
2 Cubillos-Ruiz JR, Silberman PC, Rutkowski MR, *et al*. *Cell* 2015; **161**:1527-1538.
3 Wu R, Zhang QH, Lu YJ, *et al*. *DNA Cell Biol* 2015; **34**:6-18.
4 Bolhassani A, Javanzad S, Saleh T, *et al*. *Hum Vaccin Immunother* 2014; **10**:321-332.
5 Cubillos-Ruiz JR, Engle X, Scarlett UK, *et al*. *J Clin Invest* 2009; **119**:2231-2244.
6 Iwakoshi NN, Pypaert M, Glimcher LH. *J Exp Med* 2007; **204**:2267-2275.
7 Osorio F, Tavernier SJ, Hoffmann E, *et al*. *Nat Immunol* 2014; **15**:248-257.
8 Pearce EJ, Everts B. *Nat Rev Immunol* 2015; **15**:18-29.
9 Goodall JC, Wu C, Zhang Y, *et al*. *Proc Natl Acad Sci USA* 2010; **107**:17698-17703.
10 Rehman A, Hemmert KC, Ochi A, *et al*. *J Immunol* 2013; **190**:4640-4649.
11 Curiel TJ, Wei S, Dong H, *et al*. *Nat Med* 2003; **9**:562-567.