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T CELLS

Proteasome dictates CD8$^+$ T cell fate

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Activated naive CD8$^+$ T cells can divide into daughter cells that are associated with distinct immune functions. Daughter cells can have a phenotype that is predisposed towards the terminal effector subset (pre-effector; CD8^{hi}IL-2Rα^{hi}CD62L^{lo}) or towards the central memory subset (pre-memory; CD8^{lo}IL-2Rα^{lo}CD62L^{hi}). A new study now shows that proteasome activity modulates CD8$^+$ T cell metabolism and regulates cellular differentiation into these cell subsets.

The proteasome has been shown to asymmetrically segregate in CD8$^+$ T cells that are undergoing the first division in response to infection; however, it is unclear what effect this has on the fate of the daughter cells. To determine whether asymmetrical division of the proteasome machinery might affect proteasome activity and the eventual fate of the daughter cells, Widjaja *et al.* used a model in which OT-I CD8$^+$ T cells (which recognize ovalbumin (OVA)) were adoptively transferred into mice, which were then infected with *Listeria monocytogenes*-expressing OVA (Lm-OVA). Flow cytometry analyses showed that first division CD8$^+$ daughter T cells with the pre-effector phenotype had lower endogenous proteasome activity, whereas pre-memory cells had higher activity. Furthermore, CD8$^+$ T cells that had low proteasome activity expressed increased levels of molecules associated with effector functions (granzyme B and T-bet) and decreased levels of memory-associated molecules (BCL-2, IL-7Rα and TCF7).

The authors treated activated CD8$^+$ T cells that were cultured *in vitro* in IL-2 (to induce effector-like differentiation) or IL-15 (to induce memory-like differentiation) with pharmacological proteasome inhibitors and activators. Inhibiting proteasome activity in IL-2-cultured cells increased the number of effector-like CD8$^+$ T cells, whereas inhibiting proteasome activity in IL-15-cultured cells reduced the proportion of memory-like cells. By contrast, activating the proteasome in IL-15-cultured cells increased memory cell differentiation. Interestingly, anti-CD3-activated CD8$^+$ T cells that were treated with proteasome inhibitors had increased IFNγ production and expressed increased levels of the effector cell transcription factors T-bet and interferon regulatory factor 4 (IRF4). Moreover, CD8$^+$ T cells treated with a proteasome inhibitor showed increased killing of target cells in cytotoxicity assays. These results suggest that proteasome inhibition enhances effector but reduces memory CD8$^+$ T cell differentiation. Importantly, an *in vivo* model recapitulated the *in vitro* findings: mice that were infused with proteasome inhibitor-treated OT-I CD8$^+$ T cells and then infected with Lm-OVA showed reduced formation of memory CD8$^+$ T cells. In contrast, pretreating OT-I CD8$^+$ T cells with proteasome activators enhanced the generation of memory CD8$^+$ T cells.

Microarray analyses of CD8$^+$ T cells treated with proteasome inhibitors showed an enrichment for effector cell gene sets, whereas proteasome activator-treated cells were enriched for memory cell gene sets. Furthermore, proteasome modulation substantially affected pathways relating to metabolic processes, which was confirmed by stable isotype labelling by amino acids in cell culture (SILAC). Notably, *in vitro* proteasome inhibition of CD8$^+$ T cells increased glycolytic activity (a characteristic of effector cells), and proteasome activation increased oxidative phosphorylation (a characteristic of memory cells). Last, the authors found that the metabolic changes induced by proteasome modulation were mediated, in part, by the MYC transcription factor. In summary, proteasome activity can modulate the fate and function of CD8$^+$ T cells.

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> “daughter T cells with the pre-effector phenotype had lower endogenous proteasome activity”

ORIGINAL ARTICLE Widjaja, C. E. *et al.* Proteasome activity regulates CD8$^+$ T lymphocyte metabolism and fate specification. *J. Clin. Invest.* http://dx.doi.org/10.1172/JCI90895 (2017)