Cell

Mitochondrial Networking in T Cell Memory

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T-lymphocytes show large changes in ATP demand and nutrient utilization, imposed by their different roles as T memory and T effector cells. Therefore, T cell remodeling represents a bioenergetic challenge to mitochondria. New work from Buck et al. links changes in mitochondrial shape to T cell fate choice.

Mitochondria change size, shape, and cellular location. Mitochondrial dynamics refers to the mechanisms regulating these changes, as this organelle moves around the cell and engages in fusion and fission events. This dynamism plays a role in organellar quality control and in the adaptation of mitochondria to changes in bioenergetics parameters, such as energy demand, nutrient supply, and energy efficiency (Liesa and Shirihai, 2013; Wikstrom et al., 2014). In this context, T cell activation represents a uniquely valuable system in which changes in nutrient preferences and energy demand have been documented. T effector cells (T_E) respond to antigen recognition with an increase in lactate production through glycolysis as well as an increase in aerobic ATP production by the mitochondria (Sena et al., 2013). Once the antigen is cleared, some T effector cells become T memory cells (T_M), which switch their nutrient preference to fatty acids and utilize mitochondrial beta oxidation to sustain bioenergetic demand (Pearce et al., 2013). Buck et al. (2016) addresses the question of whether this marked change in nutrient preference and underlying mitochondrial dynamics contribute to these changes in preference and T cell fate.

Looking at mitochondrial morphology in T_E and in T_M cells by electron and fluorescence microscopy in the context of an infection model, Buck et al. (2016) observed elongated mitochondria as well as an increase in total mitochondrial mass in T_M cells, as compared to T_E cells. These changes had been previously seen by O'Sullivan et al. (2014) using electron microscopy, but the mechanisms involved were not clear. Buck et al. (2016) observed that the differences in morphology were associated with changes in Drp1 phosphorylation status (Ser616) and, therefore, with the inhibition of mitochondrial fission in T_M cells and with the activation of fission in T_E cells (Figure 1). Measurements of mitochondrial mass reflect a balance between de novo biogenesis and mitochondrial removal by mitophagy. Previous studies showed that mitochondria elongate during activation of autophagy, which prevents their removal by mitophagy under conditions requiring efficient ATP production (Gomes et al., 2011). It may be then that the differences in mitochondrial mass observed between the T cell types could be explained by inhibition of mitophagy in T_M cells.

Next, Pearce and colleagues explored the role of mitochondrial fusion in T_M and T_E bioenergetics changes and in immune cell function. Opa1, Mfn1, and Mfn2 are proteins executing mitochondrial fusion, but also have additional functional roles. In this T cell context, Pearce and colleagues show that loss of Opa1, but not Mfn1 or Mfn2, decreased survival of T_M lymphocytes, which was associated with altered cristae structure and decreased spare respiratory capacity. Importantly, T_E cells could be shifted to a T_M fate and accordingly change their nutrient preference to fatty acid oxidation by elongating mitochondria either by Opa1 overexpression or the combined treatment with two compounds, one that blocked fission (Mdivi1) and one promoting fusion (M2) (Figure 1).

Despite the effects on mitochondria structure induced by Opa1 overexpression and the 2-compound treatment, elongated morphology is not essential for T_M cell identity, nor for mitochondrial fatty acid oxidation. This is demonstrated by the absence of changes in survival observed in T_M cells lacking Mfn1 or Mfn2 and by normal fatty acid oxidation rates in T_E cells lacking Opa1. These results recall previous studies in brown adipocytes showing that the capacity to oxidize fatty acids requires mitochondrial fragmentation mediated by the activation of Drp1 and by the inactivation of Opa1 fusion activity through proteolysis (Wikstrom et al., 2014). Altogether, these studies demonstrate that the relationship between mitochondria morphology and fatty acid oxidation is both dependent on the cell type, the cellular demand for mitochondrial ATP synthesis, and the molecular mechanisms used to modulate mitochondrial morphology.

In this context, blocking fission, while elongating mitochondria, is expected to stop mitochondrial removal of damaged mitochondria by mitophagy (Twig et al., 2008). This is important to mention, as there are multiple studies demonstrating that blocking Drp1-mediated fission decreases mitochondrial respiratory capacity (Twig et al., 2008) likely shifting nutrient preference to lactate-generating glycolysis. However, Buck et al. (2016) found that T cells treated with pro-elongation compounds, including fission inhibitors, show enhanced mitochondrial respiratory capacity. These seemingly contradictory findings can be reconciled in that T_M cell behavior could be similar to cellular senescence, which is associated with mitochondrial elongation (Yoon et al., 2006). Senescent and dormant cells (such as T_M cells) have in common that they might not have large requirements for mitochondrial turnover/mitophagy, as they do not replicate and usually slow down their absolute

metabolic rates. However, both senescent and dormant cells still have a demand for efficient ATP synthesis per nutrient. In the case of senescent cells, the reason for this demand is that overall mitochondria capacity has declined with time, and in the case of T_M cells (dormant), the reason is that their activity is not required until the antigen is present again. Thus, dormant T_M cells are likely adapted to use the minimum amount of resources/nutrients to maintain themselves.

Of interest, the effects of adding a fusion activator and a fission inhibitor in vitro on T_E cells were maintained 12 days after the cells were transferred to mice, and therefore, effects on T_M function were maintained in the likely absence of the pro-elongation compounds. This finding suggests that inhibiting fission at a certain stage in T_E cell development might send a retrograde signal to the nucleus to permanently transform a T_E into a T_M cell and to change their mitochondria protein composition to support fatty acid oxidation.

The study by Pearce and colleagues demonstrates a novel role for factors that control mitochondrial dynamics components in the metabolic remodeling of T cells. We believe that this model will advance understanding not only of mechanisms of T cell metabolic remodeling, but will also inform the study of the relationship between mitochondrial dynamics, nutrient preference, and mitophagy. It also opens the way for probing mechanisms tying mitochondrial retrograde signaling to mitochondrial morphology to determine permanent changes in cell metabolism regulation.

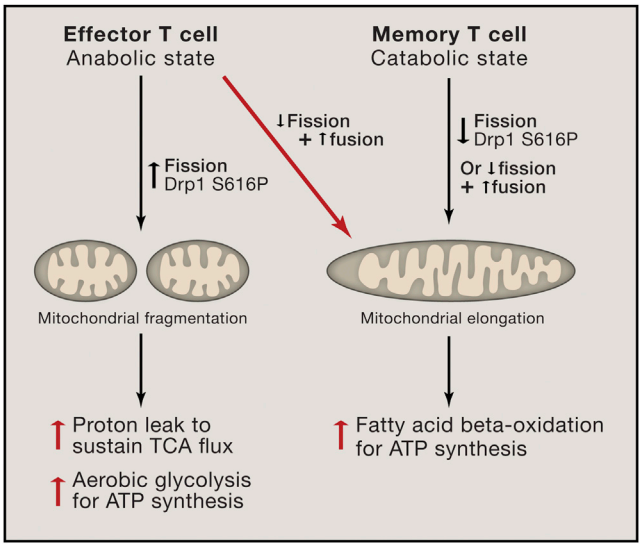

Figure 1. Mitochondrial Morphology Determines T Cell Fate

Effector T cell (T_E) development involves activation of mitochondrial fission and subsequent fragmentation, regulated by Drp1 phosphorylation in serine 616. Memory T cell (T_M) development involves inhibition of mitochondrial fission, leading to mitochondrial elongation, by decreasing Drp1 phosphorylation. The opposed mitochondrial morphologies, fragmented versus elongated, are associated with different bioenergetic requirements. Mitochondrial fragmentation in anabolic T_E cells is associated with increased proton leak (respiration not coupled to ATP synthesis). Fragmentation and leak allows increasing TCA cycle flux for anabolism in a context of increased aerobic glycolysis and high ATP/ADP ratio, which inhibits coupled, but not uncoupled, respiration. T_M cells are catabolic and do not require TCA cycle intermediates for anabolism. As a consequence, T_M cells oxidize fatty acids, which can provide more ATP per molecule of nutrient oxidized. Induced changes in mitochondrial structure can shift T_E cells to a T_M cell phenotype, which has implications for T cell manipulation in therapeutic contexts.

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