Mitochondria apply the brake to viral immunity

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Abstract

The development and function of Cytotoxic CD8 T cells (CTL), which provide immunity to viral infections, are regulated by changes in mitochondrial respiration. Champagne et al., describe a new mechanism through which mitochondrial metabolism controls production of ATP required for the secretion of critical anti-viral molecules by CTL.

The recognition of antigen results in the rapid expansion and differentiation of CD8 T cells into CTL, which either directly kill virally infected cells or secrete cytokines that orchestrate both antibody and cell mediated immunity. Following this so-called effector phase, an equally dramatic decrease in the number of CTL follows (contraction phase), which is driven by apoptosis. A small subset of CTL escape apoptosis and differentiate into memory CD8 T cells, which provide long-term immunity to virus through robust recall responses, should an individual encounter the same pathogen (Ahmed and Gray, 1996; Opferman et al., 1999). Memory cells revert to a quiescent phenotype in which slow cell turnover allows them to persist for several years. Over the past few years important insights have been gained into the metabolic changes that occur in CD8 T cells to drive these dramatic differentiation events. It is widely accepted that glycolysis is the main source of ATP for the expansion of CTL and that the turnover of quiescent naïve and memory cells, is more dependent on oxidative phosphorylation (OXPHOS) in mitochondria (Pearce and Pearce, 2013). However, more recent work has revealed a role for OXPHOS in the expansion of both CD8 T cell (Okoye et al., 2015) and CD4 T cell (Sena et al., 2013) effectors. Therefore it is clear that mitochondrial output is required not only for the maintenance of naïve and memory T cells but also the rapid expansion of CTL effectors. In *Immunity,* the paper by Champagne et al. (Champagne et al., 2016) describes a new level of control of mitochondrial respiration over CTL immunity to influenza infection.

Methylation-controlled J protein (MCJ/DNAJC15) is a member of the DNAJ family of chaperones and is located within the inner mitochondrial membrane (IMM) of CD8 T cells (Hatle et al., 2013). The activity of mitochondrial OXPHOS is enhanced by the assembly of electron transport chain (ETC) super complexes containing Complexes (C) I, III and IV, which facilitate the efficient transfer of electrons resulting in increased mitochondrial membrane potential (MMP) because of reduced electron

leakiness (Acin-Perez et al., 2008). MCJ interferes with the formation of these super complexes, thereby inhibiting CI activity and lowering MMP (Hatle et al., 2013). Using MCJ KO mice, Champagne et al., show that MCJ acts as a negative regulator of mitochondrial respiration in CD8 T cells. Effector CTL deficient in MCJ exhibited higher levels of CI-CIII-CIV super complexes and increased OXPHOS (as indicated by elevated oxygen consumption and MMP) (**Figure 1**). This resulted in increased output of mitochondrial ATP. However, MCJ deficiency did not affect CTL proliferation or activation but rather an increase in mitochondrial ATP specifically increased the secretion of the key the effector cytokines IFN-γ and IL-2. Importantly, MCJ deficient CD8 T cells gave rise to increased protective responses to influenza virus even though there was no increase in the level of primary CTL after initial challenge of secondary CTL in recall memory responses. The increase in virus clearance was likely due to qualitative increases in CTL immunity afforded by increases secretion of IFN-γ and the exocytosis of cytotoxic granules – both of which are ATP consuming processes (**Figure 1)**.

That MCJ acts as a break on CTL effector function was convincingly demonstrated by the authors. MCJ controlled effector function, not at the level of cell proliferation or activation, but rather at the level of effector function. Lymphocyte Expansion Molecule (LEM) is a recently described positive regulator of OXPHOS that controls CTL immunity, not at the level of effector molecule secretion, but rather at the level of cell proliferation, through the production of mitogenic, mitochondrial Reactive Oxygen Species (mtROS) (Okoye et al., 2015). In general, increased MMP results in increased mtROS (Korshunov et al., 1997), but the increase in MMP brought about by MCJ deficiency is due to increased super complex formation, which would prevent electron leakiness and mtROS formation. This lack of increased mtROS production may well be an explanation why MCJ deficiency does not result in increased CD8 T

cell activation and proliferation. This would be consistent with the role ascribed to MCJ in increasing MMP through super complex formation in other energy demanding tissues (such as the heart) without concomitant increase in damaging mtROS (Hatle et al., 2013). However, the role of MCJ in tumours is less clear because MCJ deficiency does not affect proliferation (Hatle et al., 2013).

ATP is the mitochondrial export that mediates MCJ effects on CD8 T cell function. The authors show microenvironments of high ATP (derived from OXPHOS) located in cytosolic locations consistent with energy dependent secretion of cytokines. Another interesting immune-specific role for ATP involves the secretion of mitochondrial ATP from T cells, where it acts in an autocrine-stimulatory fashion (Ledderose et al., 2014). Thus, the findings of Champagne et al. further support the view that mitochondrial ATP has important signalling properties in T cells.

Immunity to influenza was increased by MCJ deficiency and so the question remains as to the physiological role of MCJ in CD8 T cells. Conventional wisdom would predict that the brake provided by MCJ on CD8 T cell effector responses would protect the host from immuno-pathology, which can be tested in mouse models of chronic viral infection. MCJ deficiency resulted in increased secretion of IFN-γ, and cytotoxic granule exocytosis, which correlated with increased clearance of influenza. It will be interesting to determine what arms of the adaptive immune response are activated by the increase output of IFN-γ resulted and which cytotoxic effector molecule is responsible for the presumed increase in CTL killing.

An additional role of MCJ DNAJC15 in the import of proteins into the mitochondria is possible, based on the function of related proteins in yeast and insects (Hatle et al., 2013). In yeast, the ortholog of mammalian DNAJC19, which is highly homologous to

MCJ DNAJC15, is Tim14 - a component of the IMM translocase that also interacts with CIII and CIV. Therefore, it is possible that MCJ may control OXPHOS activity not only at the level of super complex formation but also at the level of protein import and re-folding.

In summary, Champagne et al., have described a new way in which mitochondrial output is regulated in CD8 T cells. Although the molecular details of how the membrane-anchored, MCJ chaperone interferes with super complex formation remains to be determined, the paper points to MCJ as a new target to turn-on useful CTL immunity. Inhibition of MCJ activity or expression may therefore provide a new way of enhancing CTL immunity to viruses and cancer through the re-programming of mitochondrial metabolism. In addition, MCJ inhibition may lead new ways to reduce pathological accumulation of lipids through the induction of mitochondrial respiration and lipid catabolism.

1156 words.

Selected Reading

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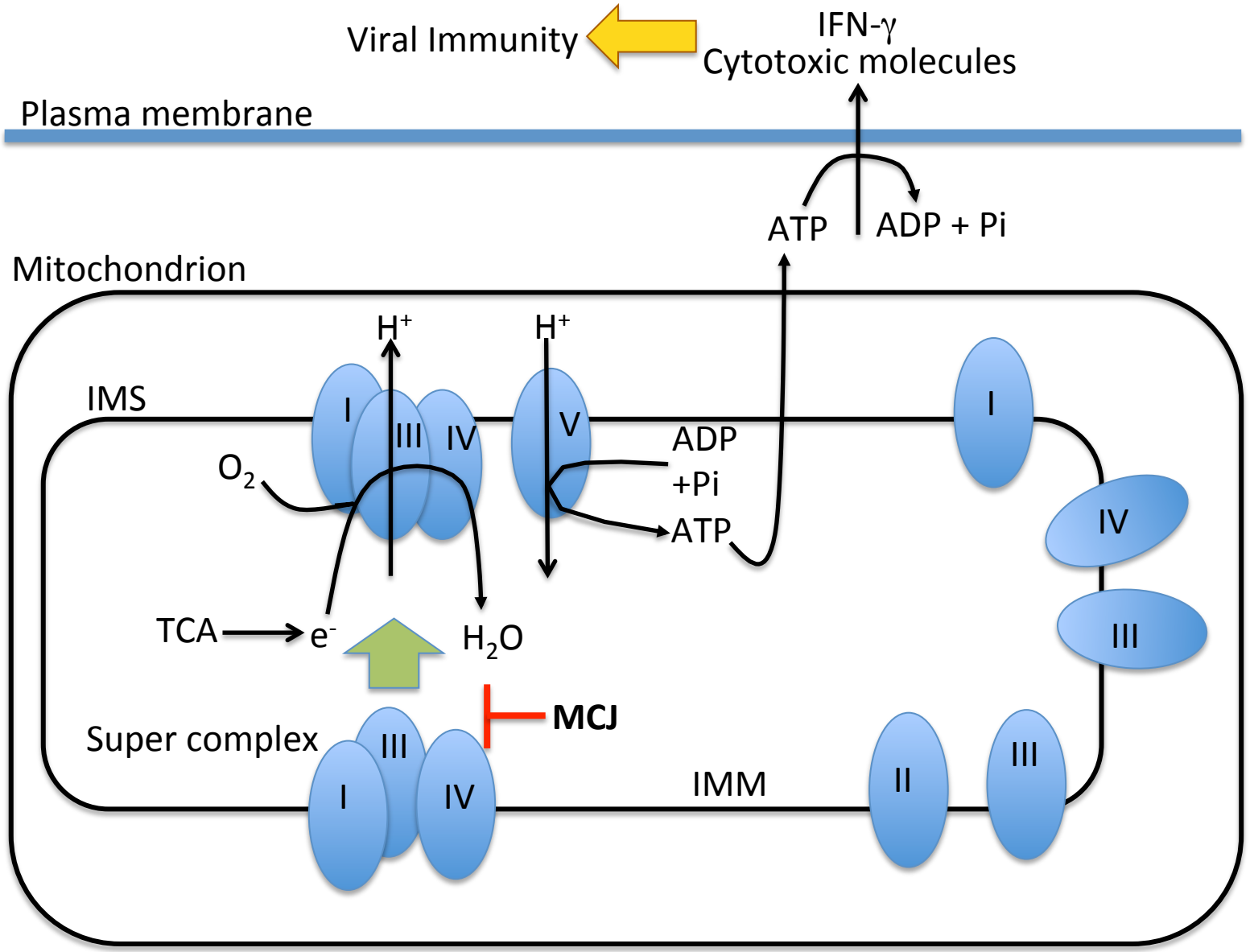
Figure 1 Legend

The mechanism of MCJ action in CD8 T cells. Super complexes form between CI, CIII and CIV of the ETC in the inner mitochondrial membrane (IMM) and facilitate the transfer of electrons from reduced substrates produced by the Tricarboxcylic acid (TCA) through CI, CIII and CIV to O_2 as the final acceptor and the transfer of H^+ into the intermembrane space (IMS). The resulting chemiosmotic gradient results in the flow of H^+ from the IMS through CV and the production of ATP from ADP +Pi. Mitochondrial ATP is hydrolysed to yield energy for the active secretion of cytokines (e.g. IFN-γ) and the exocytosis of cytotoxic molecules from CD8 T cells. MCJ interferes with the formation of super complexes and so impairs ETC and the production of ATP by OXPHOS resulting in decreased secretion of effector molecules and anti-viral immunity.


Viral Immunity
IFN-γ
Cytotoxic molecules
Plasma membrane
ATP
ADP + Pi
Mitochondrion
IMS
H+
H+
I
III
IV
V
O2
ADP
+Pi
ATP
TCA
e-
H2O
MCJ
Super complex
IMM
I
IV
III
II
III