Asymmetric rejuvenation of mitochondria guides the differentiation for effector and memory cells

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In an immune response, naive or memory lymphocytes give rise to terminally differentiated antibody-secreting plasma cells to provide function while also regenerating less differentiated memory lymphocytes. However, it remained unclear how production of differentiated lymphocytes is coupled to renewal of the progenitor cell. Here we provide evidence that asymmetric inheritance of healthy or aged mitochondria contributes to the generation of functional distinct daughter cell. We proposed a model that differentiating into effector cells may represent an accelerated aging phenomenon. The daughter cells that accumulate more old mitochondria tend to become effector cells, whereas the memory population maintains stem cell-like differentiation potential and self-renewal ability by asymmetric rejuvenation of mitochondria.

We showed that the healthy status of mitochondria is a timer for effector cell differentiation. Modulation of mitochondria function by pharmacological and genetic targeting of Drp-1 protein, which participated in mitochondrial renewal, accelerated the switching of transcriptional program to effector cells. For B cells, Mdivi-1 (Drp-1inhibitor) treatment or retrovirally expressing dominant negative Drp-1 (Drp1 K38A) in B cells increased IRF4-mediated Pax5 repression and differentiation into plasma cells.

Moreover, we found the linkage between mitochondria function and repressing of Pax5 involved reactive oxygen species (ROS) production and AMPK mediated quality control mechanism. ROS scavenger treatment increased the memory-like population ($Pax5^{hi}$, $IRF4^{low}$) and suppressed the differentiation of effector subsets ($Pax5^{low}$, $IRF4^{hi}$) in Mdivi-1 or Drp-1 K38A treated B cells. In addition, the AMPK knock cells tend to differentiate into effector cells, and they were more sensitive to Mdivi-1 induced Pax5 down regulation.

The nature source of the mitochondria stress comes from accelerated aerobic glycolytic after lymphocytes been activated. Over-expression of hexokinase hexokinase 2, which is one of the rate limited enzymes in glycolysis, resulted in Pax5 down regulation. By contrast, inhibiting glycolysis by 2-DG (a nonmetabolizable glucose analog) is sufficient to cancel the effect of Mdivi-1 in Pax5 repression. In sum, enhancing glycolytic pathway boosts effector cell differentiation, whereas suppressing glycolytic pathway helps to retain the self-renewal activity of activate lymphocytes.

Collectively, these evidence reveals mitochondria not only involved reprogramming metabolic pathways but also switching of transcriptional program. Thus, the metabolic status is an integrated part of the signaling pathway guiding the differentiation of lymphocytes, rather than the result of switching transcription program.