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Related Content

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J Immunol (May,2017)

Ubc9 Is Required for Positive Selection and Late-Stage Maturation of Thymocytes

J Immunol (May,2017)

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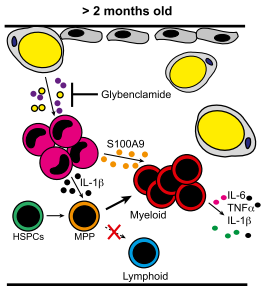
Accelerated Aging in Young Rabbits Models Old Bone Marrow

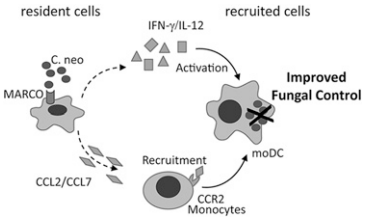


In humans and mice, aging bone marrow (BM) exhibits a decline in B lymphopoiesis that is associated with an increase in BM fat, an inflammatory environment, and a hematopoietic shift toward myelopoiesis. Previous experiments in rabbits, in which B lymphopoiesis arrests at a young 2–4 mo of age, suggested that the age-associated decline in rabbit B lymphopoiesis is likely due to changes in the BM microenvironment, rather than changes in hematopoietic progenitors. In this issue, Kennedy and Knight (p. 3471) observed that when compared with BM from 3-wk-old rabbits, BM from 2–3-mo-old rabbits had a significant increase in fat spaces, which correlated with the arrest of B lymphopoiesis, and an increase in $CD11b^+$ myeloid cells. $CD11b^+$ cells from 2–3-mo-old rabbits also exhibited increased expression of IL-1β, a downstream effector molecule involved in adipocyte-driven inhibition of B lymphopoiesis. Culture of BM cells in media conditioned with the BM fat from 2–3-mo-old rabbits significantly decreased $CD79a^+$ B lineage cells, but also induced the generation of $CD11b^+$ cells. Consistent with data suggesting that $CD11b^+$ myeloid-derived suppressor cells (MDSCs) inhibit B lymphopoiesis, BM cultures to which purified $CD11b^+$ cells from BM fat were added generated significantly fewer $CD79a^+$ B cells relative to BM cultures containing $CD11b^-$ cells. Two other inflammatory molecules produced by adipocytes, S100A8 and S100A9, were also found to negatively regulate B lymphopoiesis and promote $CD11b^+Gr1^+$ myeloid cell development when added to BM cultures. Finally, addition of S100A9 did not inhibit B lymphopoiesis in cultures of hematopoietic stem cells, multipotent progenitors, or common lymphoid progenitors, indicating that S100A9 does not directly target B-lineage progenitors. Rather, S100A9 appeared to directly target $CD11b^+Gr1^+$ myeloid cells, as addition of S100A9 to myeloid cell cultures induced early expression of IL-1β, NLRP3, TNF-α, and IL-6, which are inflammatory mediators known to inhibit B lymphopoiesis. Thus, the arrest of B lymphopoiesis in 2–3-mo-old rabbits is associated with an increase in BM fat and myeloid cells that create an inflammatory environment similar to that seen in aged humans and mice, indicating that rabbits may be used as an accelerated model to study age-associated changes in human hematopoiesis.

cGAS Activity Starts at the Very Beginning

The human cytosolic DNA sensor cyclic GMP-AMP synthase (*h*cGAS) plays an integral role in triggering the production of type I IFNs following detection of cytosolic dsDNA during infection, inflammation, and cancer. Whereas the crystal structures of some mammalian cGAS molecules have been determined, the proteins in these solved crystals lack the less evolutionarily conserved N-terminal 160 aa residues. In this issue, Tao et al. (p. 3627) conduct structural and functional studies of the human N-terminal domain (*h*cGAS-N160) to determine its physiological function. The secondary structure of the *h*cGAS-N160 was found to be highly disordered but, upon dsDNA binding in solution, underwent structural changes that were consistent with a shift to an α-helical structure. DNA binding studies using either full length *h*cGAS (*h*cGAS-FL), *h*cGAS-N160, or *h*cGAS with the *h*cGAS-N160 deleted (*h*cGAS-d160) indicated that *h*cGAS-d160 had the weakest affinity for dsDNA, revealing that the N-terminal domain of cGAS enhances its DNA binding ability. Single-molecule imaging experiments to visualize direct interaction between cGAS and dsDNA revealed that the N-terminal domain helps *h*cGAS expand its binding range on dsDNA. Studies investigating the contribution of the N-terminal domain to the enzymatic activity of *h*cGAS demonstrated that loss of the N-terminal domain reduced the ability of *h*cGAS to produce 2′3′-cGAMP. Deletion of cGAS in HeLa cells harboring an intact DNA signaling pathway (HeLa cGAS-KO) led to a complete blockade of type I IFN production, as well as a lack of STING and IRF3 phosphorylation following DNA transfection or DNA virus infection. *h*cGAS-FL was also found to activate STING/IRF3-dependent signaling more strongly than *h*cGAS-d160 in response to DNA virus infection. In summary, this study demonstrates that the N-terminal domain of human cGAS plays an important role in facilitating the binding efficiency of *h*cGAS to dsDNA and endows *h*cGAS with both greater enzymatic activity and activation of STING/IRF3-mediated cytosolic DNA signaling.

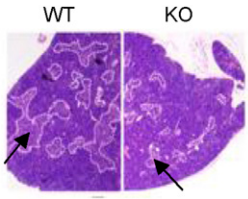
MARCO Modulates Mononuclear Cells



Although the scavenger receptor macrophage receptor with collagenous structure (MARCO) has been demonstrated to participate in phagocytosis of some fungal pathogens, whether MARCO modulates innate immune responses during cryptococcal infection is unknown. In this issue, Xu et al. (p. 3548) demonstrated that *marco* was significantly upregulated in pulmonary leukocytes from mice 4 d post *Cryptococcus neoformans* infection relative to uninfected controls. $MARCO^{-/-}$ mice suffered an increased pulmonary fungal load 7 d postinfection when compared with wild-type (WT) controls, indicating that MARCO is important during the early phase of infection. Quantification of pleural leukocytes at 4 and 7 d postinfection revealed that, when compared with WT controls, $MARCO^{-/-}$ mice demonstrated

reduced accumulation of monocytes and dendritic cells (DCs), the latter a result of decreased recruitment of monocyte-derived dendritic cells (moDC) to the lungs. Additionally, MARCO deficiency impaired the expression of *ccl2*, *ccl7, IFN-γ, IL-12b,* and *IL-17A* in lung leukocytes, molecules whose upregulation post *C. neoformans* infection is required for monocyte and moDC accumulation and control of fungal growth. Although MARCO was required for phagocytosis of *C. neoformans* by mononuclear cells, MARCO deficiency had no direct effect on the fungicidal activity of macrophages and DCs upon culture with *C. neoformans* and stimulation with IFN-γ. These data indicate that MARCO expression modulates fungicidal activity indirectly by regulating pulmonary monocyte and DC recruitment and inflammatory cytokine production during the afferent phase of *C. neoformans* infection. This study offers further insight into innate anti-cryptococcal defenses that could aid the development of supportive therapies for the treatment of cryptococcosis in immunocompromised patients, for whom currently available treatments are generally ineffective.

SUMOylation Supports SP Thymocytes



Posttranslational protein modifications via attachment of the small ubiquitin-like modifier protein (SUMO) to lysine residues influence numerous biological processes. This SUMOylation process is centrally controlled by UBC9, an E2 protein that transfers the SUMO moiety to protein substrates. Although SUMOylation has been demonstrated to play a role in the activity of regulatory T cells, its involvement in early T cell development remains unclear. To address this gap in our knowledge, Wang et al. (p. 3461) generated mice with conditional T cell-specific deletion of *Ubc9* which was initiated in double positive thymocytes and resulted in inactivation of all SUMOylation in these cells. Numbers and frequencies of $CD4^+$ and $CD8^+$ single-positive (SP) thymocytes were reduced in these $Ubc9^{fl/fl}$ *Cd4Cre* mice, compared with littermate controls, as were numbers of T cells in peripheral lymphoid organs. These deficiencies were found to be due to a cell-intrinsic defect in the maturation step of positive selection in *Ubc9*-deficient thymocytes. In contrast, normal numbers of *Ubc9*-deficient thymocytes were observed early in thymic development, and negative selection and CD4/CD8 lineage commitment processes were intact. Further analysis of the SP thymocytes in $Ubc9^{fl/fl}Cd4Cre$ mice revealed that these cells had impaired TCR-driven proliferative capacity and increased levels of apoptosis, defects that in CD8 SP thymocytes were linked to reduced expression of IL-7Rα. Although numerous TCR signaling components appeared unaffected by *Ubc9* deletion in $Ubc9^{fl/fl}Cd4Cre$ thymocytes, SUMOylation was found to be important for NFATc1 entry into the nucleus, a translocation event that is involved in thymocyte proliferation and maturation. Taken together, these data indicate an important role for SUMOylation in T cell development via participation in thymic positive selection and late-stage thymocyte maturation.