P.A1.02.21
Long-term effects of microglial depletion on tau pathology and spatial memory

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A hallmark of Alzheimer's disease pathology is neurofibrillary tangles comprising hyper-phosphorylated tau. Microglia are resident myeloid cells of the CNS that are implicated in neuro-inflammatory and neurodegenerative disorders. To investigate the reciprocal relationship between microglia and tau pathology we first characterized the microglial response in a mouse model of progressive tau accumulation (hTau mice). We did not detect changes in microglia surface receptor expression, proliferation, cytokine production, morphology or transcriptional profile in aged hTau mice indicating a lack of pathogenic microglia responses to tau aggregation. To assess the direct impact of microglia on tau pathology and associated neurological deficits we developed a protocol for long term microglial depletion in $CX3CR1^{CreER}R26^{DTA}$ mice and crossed them with hTau mice. We then depleted microglia for 3 months which resulted in exacerbation of spatial memory function. These results indicate that microglia have a neuroprotective role during Alzheimer's related tau pathology.

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Newborn babies have high number of immature *monocytes expressed CD116* in peripheral blood than adults

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Monocytes are able to differentiate to dendritic cells (DCs) under inflammatory situations. Different monocyte subsets show distinct inflammatory cytokine profiles and differentiation potential under steady-state and inflammatory situations. The major subset of monocytes consists of CD14-high CD16-negative (CD14++CD16−). Commited dendritic cell originated from immature monocytes. In humans (hpre-CDC) that develops from committed DC progenitors (hCDPs) in the BM. We have measured the number of immature monocytes (pre-CDC) with CD34+CD38+ CD116+ expression by flow cytometry with acquisition of a million cells from peripheral blood in 10 newborn and 10 adults. To determine the physiological distribution of hpre-CDCs in humans, we examined, peripheral blood, of newborn and adult for small numbers of pre-CDCs travel through the blood and replace cDCs in the peripheral organs, maintaining homeostasis of the highly dynamic cDC pool. Monocyte-derived circulating short-lived pre-CDCs are high in newborn (mean:57 cells/million cells) than adults (mean:7 cells/million cells). We assume that any organ includes epithelial cells, endothelial cells, fibroblasts, stromal cells, and hematopoietic cells are a source of GM-CSF secretion. Circulations of CD116+ short-lived pre-CDCs undergo maturation when going through the vascular environment with high GM-CSF secretion to microenviroment.

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Ssu72 phosphatase regulates tissue-resident macrophage function

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Dynamic alterations of phosphorylation state of many cellular signaling-mediated proteins regulate their molecular and cellular fates. Ssu72 is dual protein phosphatase that can act upon tyrosine or serine/threonine residues and transcription/RNA-processing factor. Ssu72 has been characterized as an RNA polymerase II carboxy-terminal domain phosphatase that specifically catalyses serine-5-p dephosphorylation. Recently, we reported that Ssu72 functions as a cohesin-binding phosphatase and interplays with Aurora B kinase for regulation of duplicated sister chromatid separation, and that the deletion of hepatocyte specific Ssu72 led to the development of a high incidence of fatty liver diseases. Ssu72 is known to be expressed in a tissue-specific manner, and we found that Ssu72 expressed in adipose tissue, especially strongly in brown adipose tissue. In this aspect, we generated conditional knock out mice which Ssu72 is deleted specifically in adipose tissue and found that the deficiency of Ssu72 leads to BAT dysfunction compared to wild type mice. Interestingly, we observed not only dramatically reduction of macrophage population but also defective M2 macrophage generation in Ssu72-deficient BAT. Thus, we further generated myeloid cell specific Ssu72 knockout mouse model. This study will include the physiological relevance of Ssu72 loss-of-function in tissue-resident macrophage.

P.A2.01 Immune development and aging from the cradle to the grave - Part 1

P.A2.01.01
Differential Recovery Of Intrathymic Microenvironments That Follows Thymus Damage Results In Qualitative Changes In T-cell Reconstitution

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Following ablative therapies used for cancer treatment, damage to the thymus disrupts it ability to support T-cell development. This results in delayed T-cell reconstitution and a period of immunodeficiency that leaves patients susceptible to potentially fatal infections. Thus, examining mechanisms that control thymus regeneration, and identifying new approaches to boost thymus recovery, are important in devising new therapeutic strategies to improve immune reconstitution.
We have used sub-lethal irradiation (SLI) in a mouse model of thymic injury, and performed systematic examination of the recovery of both thymocytes and the thymic microenvironment. Following SLI, we find the generation of $CD4^+CD8^+$ thymocytes and their $CD4^+$ and $CD8^+$ progeny occurs in two distinct waves. Analysis of early thymic progenitors indicates that while an initial and transient wave of recovery occurs via a radioresistant intrathymic progenitor, a second sustained wave occurs via thymus entry of bone marrow progenitors. Surprisingly, concurrent analysis of the thymic microenvironment indicates cortial thymic epithelial cell numbers remain constant, suggesting they are radioresistant and available to support thymocyte development. In contrast, medullary thymic epithelial cells and dendritic cells are depleted following damage. Consistent with this, recovery of medulla-dependent $Foxp3^+$ regulatory T-cells occurs after the generation of conventional $CD4^+$ thymocytes.
In summary, our findings suggest that following damage, distinct thymic areas show differential recovery kinetics that impact upon the quality of new T-cell production. Ongoing studies are examining whether known regulators of thymus recovery, including KGF and LTβR stimulation, can restore medullary microenvironments to ensure balanced recovery of T-cell development.

P.A2.01.02
Effect of IL-15 cytokine on the adhesion and migration properties of CD4+CD28null T-lymphocytes in rheumatoid arthritis patients

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CD4+CD28null T-lymphocytes are cells with terminal differentiation that appear after repeated antigenic stimulation and are found at high levels in patients with rheumatoid arthritis (RA). The main objective of this work was to study the adhesion and migration capacity of these cells and the effect of the cytokine IL-15 on these properties. The experiments were performed with peripheral blood samples from patients with RA, where the CD4+ T-lymphocytes were isolated. To study the adhesion ability of CD4+CD28null cells CD11a, CD49d, CD44, CCR5 and CX3CR1 molecules were studied by flow cytometry. The basal level of all these molecules was higher in CD4+CD28null T-lymphocytes. Moreover, IL-15 induced a significant increase in CD11a and CD44 in CD4+CD28null T-cells. Cell migration was studied in CD4+ T lymphocytes isolated and cultured in "transwell". Migrated cells were significantly higher in the wells with IL-15 and the majority of these cells were CD4+CD28null. This effect was IL-15 dose and time dependent. We also studied the activation and activity of Rho A, Rac 1 and Cdc42, proteins involved in cell migration. Both the basal levels of Rho A and the activated RhoA, Rac1 and Cdc42 were clearly higher in CD4+CD28null T-cells. In conclusion, CD4+CD28null T-cells exhibited very different migratory and adhesion properties compared to CD4+CD28+ T-cells in AR. This could be interesting when designing different therapeutic targets to try to prevent the migration and accumulation of these cells in locations where they could exert a pathogenic function and thus, slow down the progression of the disease.