M-CSF-mediated macrophage development is dominantly inhibited by NOD2 signaling for replenishment of immunogenic dendritic cells

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DOI: 10.1002/eji.202170200

POSTER PRESENTATIONS

P-0672

M-CSF-mediated macrophage development is dominantly inhibited by NOD2 signaling for replenishment of immunogenic dendritic cells

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Despite recent advances, it remains unclear whether monocyte-derived dendritic cells (moDCs) represent alternative context-dependent fate in the gut. We found here that Nod2-dependent sensing of bacteria lowers the ability of circulating monocytes to respond to M-CSF for generating moDCs. Such inhibitory effect on monocyte-to-macrophage transition was prevented upon blockade of TNF-α. Recognition of the gut microbiota by Nod2 was sufficient to promote the expansion of moDCs within the colonic mucosa. A competitive bone marrow transplant model further demonstrated that Nod2 promotes the conversion of monocytes into dendritic cells. Equally of importance, tumours with the highest transcript levels of NOD2 were associated with a favorable prognosis and characterized by an enrichment of a gene signature related to moDCs. This study implicates that Nod2-dependent sensing of the gut microbiota influences monocytic lineage commitment into dendritic cells, which sets the stage for future investigations to achieve accurate outcome prediction in colorectal cancer.

Keywords: Immune development, macrophage, dendritic cells, *in vivo* tumor models

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Ex situ heart perfusion and standard of care cold storage differentially affect the ischemic secretome of donor hearts in perfusates but not the reperfusion response in recipient plasma

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Allograft preservation procedures may influence the donor organ status and in turn affect heart transplant (HTx) recipient. Here we aimed to compare the secretomes in recipient plasma and perfusates in patients whose hearts were either preserved using *ex situ* heart perfusion (ESHP) or standard of care (SOC) cold static preservation in order to identify potential biomarker candidates for heart preservation. Using multiplex techniques, we measured 50 cytokines/chemokines in recipient plasma before (pre), after (T0), 24h and 3 weeks after HTx. Unsupervised cluster analyses identified top-10 plasma cytokines and chemokines clearly separating T0 from other time points after HTx and reflecting a reperfusion injury-specific pattern. Surprisingly, ESHP or SOC heart preservation did not have a significant impact on these inflammatory plasma profiles at T0, T24 or 3 weeks. The two strongest discriminators separating T0 from other time points i.e. IFN-γ, SCGF-β were detected in both ESHP and SOC recipients at comparable concentrations. In contrast, the preservation method clearly affected the cytokine/chemokine profile in perfusates highlighted by higher concentrations of pro- (IFN-γ, CXCL10) and anti-inflmmatory (IL-10, IL-1RA) mediators in ESHP compared to SOC samples. Although ESHP or SOC preservation did not affect the reperfusion response in plasma at T0 after HTx, normothermic oxygenated preservation of donor hearts was accompanied by secretion of pro- and anti-inflammatory cytokines, chemokines that may affect long-term functionality and longevity of the graft. With a better understanding of molecular changes during ESHP, we expect to identify biomarker candidates for improved organ function pre HTx.

Keywords: Biomarkers, chemokines, cytokines and mediators, transplantation

P-0676

The role of NK cells in the resolution of malaria-associated acute respiratory distress syndrome

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Malaria is a global health disease with >400 000 deaths each year, caused by complications such as malaria-associated acute respiratory distress syndrome (MA-ARDS). Despite efficient parasite killing with antimalarial drugs, 15% of patients with complications still die. This shows the need to study resolution and wound healing mechanisms involved in the recovery from these complications. Disease resolution is coordinated by several leukocyte subtypes. Here, we investigate the role of NK cells in the disease resolution of MA-ARDS. C57BL/6 mice were infected with *Plasmodium berghei* NK65 (*Pb*NK65), resulting in the development of MA-ARDS on day 8 post infection. On this day, antimalarial treatment with artesunate and chloroquine was started for 5 days. To study the role of NK cells, NK cells were depleted by injection of anti-NK1.1. Depletion of NK cells did not affect the development of MA-ARDS, but resulted in a decreased survival during resolution. In particular, only 50% of the anti-NK1.1-treated mice recovered from MA-ARDS upon anti-malarial treatment, compared to >80% without depletion. Interestingly, the resolution of alveolar edema occurred as efficiently in the NK cell-depleted mice that could be rescued compared to the non-depleted mice. The treatment of *Pb*NK65-infected C57BL/6 mice with antimalarial drugs serves as a good model to study the resolution of MA-ARDS. NK cells are not involved during the development of MA-ARDS, but are critical during the resolution process upon anti-malarial treatment.

Keywords: Innate host defence, NK cells, parasite infections, tissue damage and repair