An IL-10/DEL-1 axis supports granulopoiesis and survival from sepsis in early life

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ABSTRACT

Neutrophils constitute an essential first line of innate immune response against invading pathogens. During infancy, the reserves of neutrophils are limited, hence rendering neonates particularly susceptible to infections and infection-related pathologies like sepsis. Nevertheless, the regulation of neutrophil kinetics in infections during the early stages of life is still poorly understood.

The developmental endothelial locus-1 (DEL-1), is a soluble and secreted endogenous protein produced by endothelial and other tissue-resident cells. By binding on integrin molecules on the surface of leukocytes, it antagonizes their interaction with cell adhesion molecules on the endothelium, therefore impeding their transmigration and recruitment towards the sites of inflammation[1]. Regarding the role of DEL-1 in the course of inflammation, many studies indicate its anti-inflammatory nature as well as the inhibitory effect of pro-inflammatory cytokines like TNF-a and IL-17a, on its transcription[2]. However, the regulation and functional significance of DEL-1 in early life sepsis has not been studied previously.

In the present study we demonstrate that DEL-1 is elevated during the early post-natal days under normal and septic conditions in both mice and humans. In sepsis, DEL-1 plays a critical role for the survival of infant hosts, by supporting the sustained output of circulating neutrophils (emergency granulopoiesis) and controlling the tissue bacterial burden. In detail, septic DEL-1 deficient (Del-1$^{-/-}$) neonate mice display low numbers of myeloid-biased multipotent (MMPs) and granulocyte-macrophage progenitors (GMPs) in the bone marrow, resulting in neutropenia, exaggerated bacteremia, and an overall increased mortality, compared to Wild Type (Wt) counterparts. These defects are rescued by the exogenous administration of DEL-1 in septic murine neonates. We show that the high IL-10/IL-17A ratio, observed in newborn sepsis, sustains tissue DEL-1 expression, as IL-10 upregulates while IL-17 downregulates DEL-1. Accordingly, serum DEL-1 and blood neutrophils are elevated in septic adult and neonate patients with high serum IL-10/IL-17A ratio, leading to lower mortality rates. Therefore, the IL-10/DEL-1 axis promotes neonatal survival against sepsis by supporting the emergency granulopoiesis and preventing systemic neutropenia and bacteremia[3].

References

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