Multilevel control of dendritic cell homeostasis by ADAM10-mediated ectodomain shedding

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Sentinel dendritic cells (DC) act at the interface of innate and adaptive immunity, and are paramount for the initiation of immune responses against invading pathogens. The DC family displays high functional heterogeneity in order to orchestrate immune responses specifically tailored towards a given immunological threat. In mouse and man, conventional DC (cDC) can be separated into functionally distinct cDC1 and cDC2 populations, initially according to their phenotype and molecular signatures, and later through their ontogeny and unique transcription factor dependency. Despite these recent advances in understanding DC development and function, numerous molecular cues regulating the fine-tuning of DC homeostasis and activation are still unclear.
Members of the 'A-disintegrin-and-metalloproteinase' (ADAM) family are involved in post-translational protein modifications. Via a process called ectodomain-shedding, i.e. the release of extracellular domains of membrane-associated proteins, ADAMs control the activity, localization and interaction of different cell adhesion molecules and cytokine/chemokine receptors. Although cDC express ADAM10 in concert with many of its putative targets, it remains elusive how and to what extent ADAM10 governs critical aspects of DC biology.
To address these questions, we generated mice lacking functional ADAM10 on myeloid cells, including cDC, by crossing ADAM10flox/flox with CD11c-Cre mice. Steady state analysis revealed that cDC are uniquely sensitive to the loss of ADAM10-mediated ectodomain-shedding, as we observed a significant reduction of particularly splenic CD11b+ESAM+ cDC2 in these mice while other myeloid cell populations were not affected. One of the relevant pathways disturbed by ADAM10 deficiency is Notch signaling, which has been shown before to be essential for CD11b+ESAM+ cDC2 homeostasis.
In conclusion, we identified ADAM10-mediated ectodomain-shedding as an essential post-translational regulatory switch that controls fundamental aspects of cDC homeostasis and function. In ongoing experiments we are further dissecting the molecular underpinnings of ADAM10 to govern cDC biology in the steady state and during inflammation.

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