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DOCK8 is a regulator of T cell migration and CD4$^+$ effector T cell differentiation

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Abstract

The initiation of an efficient adaptive immune response requires migration and activation of lymphocytes within secondary lymphoid organs. The recently described DOCK family member DOCK8 is a guanine exchange factor for the small GTPase Cdc42, which is involved in maintaining cell polarity. DOCK8 mutations in mice result in impaired immunological synapse (IS) formation of B cells, as well as impaired germinal center formation and long-lived antibody production. In humans, DOCK8 deficiency causes chronic cutaneous viral infections as well as recurrent sinopulmonary bacterial infections, which points to defective T cell function in addition to impaired humoral immune response. Here, we investigated the function of DOCK8 during T cell migration, T cell - dendritic cell interactions, T cell activation and effector T cell differentiation. Chemotaxis assays and short time homing experiments revealed that DOCK8 participates to a minor degree in CD4$^+$ T cell migration through confined environments such as endothelial barriers. On the other hand, 2-photon intravital microscopy (2PM) analysis showed that DOCK8 deficiency had no effect on the interstitial migration velocity of T cells in the lymph node parenchyme. During adaptive immune responses, the ongoing interaction of CD4+ T cells with dendritic cells (DCs) and cognate B cells is central for the generation and maintenance of follicular helper T (Tfh) cells. Flow cytometric analysis after immunization revealed strongly decreased Tfh cell maintenance in the absence of DOCK8. In contrast to DOCK8-deficient B cells, DOCK8-deficient CD4$^+$ T cells showed normal LFA-1 translocation to the IS interface and sustained engagement with DCs in vivo, suggesting diverting functions of DOCK8 in different lymphocyte subsets. In summary, our data uncover that DOCK8 participates in CD4$^+$ T cell migration through confined environments, and for efficient maintenance of Tfh cells.

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