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## **DOCK8 is a Cdc42 activator critical for interstitial dendritic cell migration during immune response**

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### **Abstract**

To migrate efficiently through the interstitium, dendritic cells (DCs) constantly adapt their shape to the given structure of the extracellular matrix and follow the path of least resistance. It is known that this amoeboid migration of DCs requires Cdc42, yet the upstream regulators critical for localization and activation of Cdc42 remain to be determined. Mutations of DOCK8, a member of the atypical guanine nucleotide exchange factor family, causes combined immunodeficiency in humans. We show here that DOCK8 is a Cdc42-specific guanine nucleotide exchange factor that is critical for interstitial DC migration. By generating the knockout mice, we found that in the absence of DOCK8, DCs failed to accumulate in the lymph node parenchyma for T cell priming. Although DOCK8-deficient DCs migrated normally on two-dimensional surfaces, DOCK8 was required for DCs to crawl within three-dimensional fibrillar networks and transmigrate through the subcapsular sinus floor. This function of DOCK8 depended on the DHR-2 domain mediating Cdc42 activation. Importantly, DOCK8 deficiency did not affect global Cdc42 activity. However, Cdc42 activation at the leading edge membrane was impaired in DOCK8-deficient DCs, resulting in a severe defect in amoeboid polarization and migration. Therefore, DOCK8 regulates interstitial DC migration by controlling Cdc42 activity spatially.