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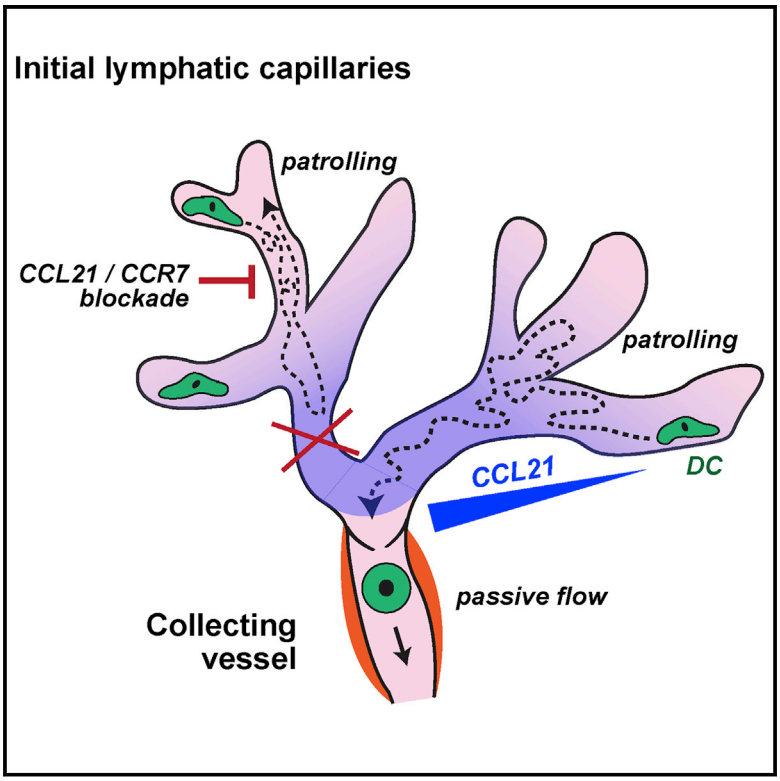
Intralymphatic CCL21 Promotes Tissue Egress of Dendritic Cells through Afferent Lymphatic Vessels

Graphical Abstract



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In Brief

Intravital microscopy studies have recently revealed that dendritic cells (DCs) migrating to draining lymph nodes actively crawl within afferent lymphatic capillaries. Here, Russo et al. provide evidence that an intraluminal CCL21 gradient, which is deposited by lymph flow, guides DCs migrating within capillaries in the downstream direction of the collecting lymphatic vessels.

Highlights

- Downstream-directed DC migration in lymphatic capillaries is lymph flow independent
- Downstream-directed DC migration in lymphatic capillaries is CCL21/CCR7 dependent
- Low flow creates a downstream-oriented CCL21 gradient along lymphatic endothelium
- The flow-induced CCL21 gradient promotes DC trafficking through afferent lymphatics

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Intralymphatic CCL21 Promotes Tissue Egress of Dendritic Cells through Afferent Lymphatic Vessels

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SUMMARY

To induce adaptive immunity, dendritic cells (DCs) migrate through afferent lymphatic vessels (LVs) to draining lymph nodes (dLNs). This process occurs in several consecutive steps. Upon entry into lymphatic capillaries, DCs first actively crawl into downstream collecting vessels. From there, they are next passively and rapidly transported to the dLN by lymph flow. Here, we describe a role for the chemokine CCL21 in intralymphatic DC crawling. Performing time-lapse imaging in murine skin, we found that blockade of CCL21—but not the absence of lymph flow—completely abolished DC migration from capillaries toward collecting vessels and reduced the ability of intralymphatic DCs to emigrate from skin. Moreover, we found that in vitro low laminar flow established a CCL21 gradient along lymphatic endothelial monolayers, thereby inducing downstream-directed DC migration. These findings reveal a role for intralymphatic CCL21 in promoting DC trafficking to dLNs, through the formation of a flow-induced gradient.

INTRODUCTION

Dendritic cell (DC) migration from peripheral tissues through afferent lymphatic vessels (LVs) to draining lymph nodes (dLNs) is essential for sustaining peripheral tolerance and for promoting immune responses against pathogens or vaccines (Förster et al., 2012; Ueno et al., 2007). Over the past 15 years, several molecular mediators of DC migration into LVs have been identified (Förster et al., 2012; Teijeira et al., 2014). Above all, the prominent role of the chemokine CCL21, which is constitutively expressed by LVs, and its DC-expressed receptor, the CC-chemokine receptor 7 (CCR7), in DC trafficking to dLNs has been recognized (Förster et al., 1999; Saeki et al., 1999). Recently, time-lapse imaging studies have provided further, cellular insights into DC migration through afferent LVs. In particular, these studies have revealed that DC trafficking through afferent LVs occurs in distinct steps. In a first step, CCR7-expressing DCs are guided toward LVs by haptotactic migration along the immobilized peri-lymphatic CCL21 gradient (Weber et al., 2013). Once in proximity of lymphatic capillaries, CCL21 also supports the docking of DCs onto lymphatic endothelial cells (LECs) (Tal et al., 2011). Subsequently, DCs enter into lymphatic capillaries by squeezing through characteristic flaps that are formed between neighboring oak-leaf-shaped LECs (Baluk et al., 2007; Pflicke and Sixt, 2009). Once within the vessels, DCs actively crawl through the capillaries (Nitschké et al., 2012; Sen et al., 2010; Tal et al., 2011). Intriguingly, DCs do not migrate completely directionally from capillaries into the downstream collecting LVs. Rather, they display a semi-directed patrolling behavior, as they frequently turn within capillaries and migrate for some time in the opposite direction of drainage (Nitschké et al., 2012; Tal et al., 2011). The final step, namely, passive transport by lymph flow, is only observed within downstream-located collecting LVs (Nitschké et al., 2012; Tal et al., 2011), likely because lymph flow in capillaries (in the order of 1–30 μm/s [Berk et al., 1996; Swartz et al., 1996]) is too low to support passive transport. Nevertheless, efficient propagation of DCs from peripheral tissues to dLNs depends on a rapid transport phase by flow, since the migratory speed of DCs within capillaries (5–8 μm/min [Nitschké et al., 2012; Tal et al., 2011]) is too slow to explain how DCs could arrive in dLNs within 6 hr to 1 day after onset of migration (Allan et al., 2006; Kissenpfennig et al., 2005). These considerations imply that active migration of DCs from lymphatic capillaries into the collecting vessels represents a rate-limiting step in the propagation of DCs to the dLN and therefore prompted us to further investigate the signals that control this process. Surprisingly, we found that DCs within lymphatic capillaries of explanted skin continued to preferentially migrate in the downstream direction, suggesting that—rather than lymph flow—chemotactic signals deposited in the vessel lumen might account for this behavior. In support of this hypothesis, we found that downstream-directed migration