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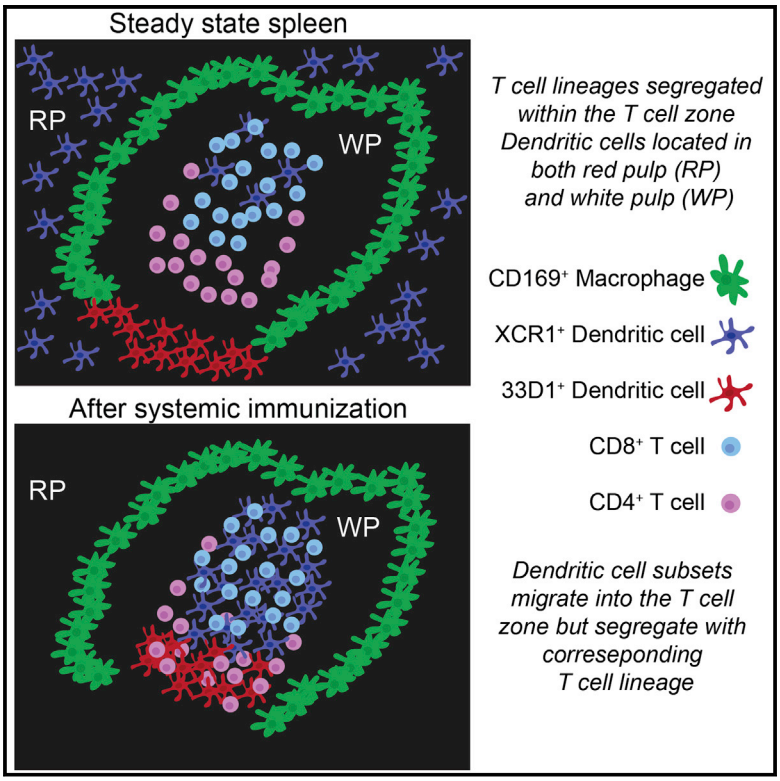
Differential Intrasplenic Migration of Dendritic Cell Subsets Tailors Adaptive Immunity

Graphical Abstract



Highlights

- CD4+ and CD8+ T cells preferentially occupy separate areas of the splenic T cell zone
- DC-intrinsic CCR7 is required for migration within the spleen after i.v. immunization
- 33D1+ and XCR1+ DCs migrate into CD4+ and CD8+ T cell areas, respectively
- Loss of DC subset and T-cell-lineage pairing abrogates either CD4+ or CD8+ T cell immunity

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In Brief

Calabro et al. demonstrate that, upon immunization, dendritic cell subsets in the spleen migrate into non-overlapping zones that correspond to regions enriched for CD4+ or CD8+ T cells. This differential migration results in the selective induction of either CD4+ or CD8+ T cell responses.

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Differential Intrasplenic Migration of Dendritic Cell Subsets Tailors Adaptive Immunity

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SUMMARY

Evidence suggests that distinct splenic dendritic cell (DC) subsets activate either CD4+ or CD8+ T cells in vivo. This bias has been partially ascribed to differential antigen presentation; however, all DC subsets can activate both T cell lineages in vitro. Therefore, we tested whether the organization of DC and T cell subsets in the spleen dictated this preference. We discovered that CD4+ and CD8+ T cells segregated within splenic T cell zones prior to immunization. After intravenous immunization, the two major conventional DC populations, distinguished by 33D1 and XCR1 staining, migrated into separate regions of the T cell zone: 33D1+ DCs migrated into the CD4+ T cell area, whereas XCR1+ DCs migrated into the CD8+ T cell area. Thus, the post-immunization location of each DC subset correlated with the T cell lineage it preferentially primes. Preventing this co-localization selectively impaired either CD4+ or CD8+ T cell immunity to blood-borne antigens.

INTRODUCTION

Activation of naive T lymphocytes is the first step in the induction of most adaptive immune responses, such as those to vaccines or pathogens. Given that this key step dictates a metabolically costly and potentially deleterious cascade of cellular events, it is not surprising that a coordinated series of checkpoints exist to regulate naive T cell priming. One crucial checkpoint is antigen presentation. This is accomplished primarily by mature dendritic cells (DCs) not only because they express the requisite stimulatory signals to activate naive T cells, but also because, after antigen capture from tissues and maturation by an innate immune stimulus, they efficiently migrate via lymphatics to draining lymph nodes (LNs) (Itano and Jenkins, 2003); circulation of naive T cells is restricted to such secondary lymphoid organs.

For blood-borne antigens, this entire process occurs in the spleen, which, unlike all other secondary lymphoid structures, does not contain afferent lymphatics (Bronte and Pittet, 2013). The spleen filters the blood of aging red blood cells (RBCs), as well as foreign antigens or pathogens that have gained access to the bloodstream. It is divided by function and structure into red pulp (RP) and white pulp (WP); between these two regions is the marginal zone (MZ) in mice or the perifollicular zone in humans (Mebius and Kraal, 2005). Most lymphocytes are located in the WP and reside in distinct zones, such as the T cell zone, where T lymphocytes are concentrated. The WP is where adaptive immune responses are generated to blood-borne antigens.

DCs are the primary cells in the spleen that prime T cells to antigens encountered in the blood (Meredith et al., 2012). Although the migration of tissue DCs to draining LNs is known to be a crucial step in the induction of T cell responses, it is not clear that the same holds true within the spleen (Czeloth et al., 2005; Ohl et al., 2004). The presence of CD8+ DCs in the T cell zone at steady state in both humans and mice (Idoyaga et al., 2009; Pack et al., 2008) raises the possibility that antigen transport via DC migration might not be necessary, unlike in other sites in the body, because the unique architecture of the spleen juxtaposes the antigen-exposed tissue (e.g., the MZ) with the lymphoid compartment (e.g., the WP) (Bronte and Pittet, 2013; Khanna et al., 2007). Indeed, the role of the primary DC homing receptor to LNs, CCR7, in DC movement within the spleen is debated (Czeloth et al., 2005; Gunn et al., 1999; Ritter et al., 2004; Yi and Cyster, 2013). However, the same kinds of innate stimuli that induce tissue DCs to migrate to LNs are also stimuli of DC migration within the spleen (Balázs et al., 2002; De Smedt et al., 1996; De Trez et al., 2005; Idoyaga et al., 2009; Reis e Sousa and Germain, 1999). If this relocalization is not necessary for adaptive immunity, then how is a threshold created to prevent