CCR7/Galpha12/13/RhoA axis drives dendritic cell migration and homing to lymph nodes

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Introduction: Upon activation, DCs express CCR7, sense CCL19 and CCL21 gradients and directionally migrate to lymph nodes, where they will encounter and activate T cells to initiate adaptive immune responses. As most chemokine receptors, CCR7 is a G-protein-coupled receptor known to couple to Galpha1 in order to signal. However, our data showed that CCL21-mediated migration of DCs is insensitive to Galpha1 inhibitor PTX, suggesting that signaling of CCR7 through Galpha12 and/or Galpha13 could be important for DC migration.

Objectives: To determine if CCR7 signals through Galpha12 and/or Galpha13 for DC migration.

Materials and Methods: Bone-marrow derived DCs from WT, single knockout or double knockout (DKO) animals of Galpha12 and Galpha13 proteins were generated to study this signaling axis.

Discussion and Results: CCR7 induced RhoA activation in DCs. The blockage of RhoA by C3 toxin or blockage of its downstream target ROCK by Y27632 compound compromised DC CCR7-mediated chemotaxis without affecting cell surface expression of this receptor. Using Pertussis Toxin (PTX) which ADP ribosylates Galpha1, thereby uncoupling it from receptor activation, we observed that only CCL19-mediated migration but not CCL21 is PTX sensitive, suggesting that CCR7 coupling may not be exclusive to Galpha1. Indeed, using a genetically defined mouse model for Galpha12 and/or Galpha13 depletion we show that the lack of Galpha12 or Galpha13 alone, had no or minimal effect on DC CCR7-mediated migration. However, Galpha12/Galpa13 DKO DCs were completely incapable of migrating to both CCL19 and CCL21 gradients. In addition, DKO DCs stained with CFSE and injected in the footpad of mice, presented a marked deficiency to reach the popliteal lymph node in contrast to single KO and wild type DCs demonstrating that Galpha12/Galpa13 proteins are important for DC migration in vivo.

Conclusions: Taken together our data supports a major role of CCR7/Galpha12/13/RhoA axis in DC migration and homing to lymph nodes.


Key Words: Dendritic Cell, CCR7, Chemotaxis