Autocrine CCL19 blocks dendritic cell migration toward weak gradients of CCL21 - DTU Orbit (10/12/2018)

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Background aims. Maturation of dendritic cells (DCs) induces their homing from peripheral to lymphatic tissues guided by CCL21. However, in vitro matured human monocyte-derived DC cancer vaccines injected intradermally migrate poorly to lymph nodes (LNs). In vitro maturation protocols generate DCs with high (type 1 DCs) or low (prostaglandin E2 [PGE2] DCs) autocrine CCL19 levels, which may potentially interfere with LN homing of DCs. Methods. Employing a three-dimensional (3D) chemotaxis assay, chemokine competition/desensitization studies and short interfering RNA (siRNA) against CCL19, we analyzed the effect of autocrine CCL19 on in vitro migration of human DCs toward CCL21. Results. Using human monocyte-derived DCs in a 3D chemotaxis assay, we are the first to demonstrate that CCL19 more potently induces directed migration of human DCs compared with CCL21. When comparing migration of type 1 DCs and PGE2-DCs, migration of type 1 DCs was strikingly impaired compared with PGE2-DCs, but only toward low concentrations of CCL21. When type 1 DCs were cultured overnight in fresh culture medium (reducing autocrine CCL19 levels), a rescuing effect was observed on migration toward low concentrations of CCL21 in a 3D chemotaxis assay. Finally pre-incubation with CCL19 negatively affected PGE2-DC migration, whereas silencing of CCL19 by siRNA improved type 1 DC migration. Importantly, in both cases, the effect was observed only at low concentrations of CCL21. Conclusions. Our results demonstrate that autocrine CCL19 negatively affects DC migratory potential toward CCL21, the potency difference between CCL19 and CCL21 being the underlying cause. CCL19 secretion level of in vitro matured DCs is an important indicator of DC vaccine homing potential.