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Response to Comment on "CXCL9 Causes Heterologous Desensitization of CXCL12-Mediated Memory T Lymphocyte Activation"

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We read with interest the recent study by Giegold and colleagues (1) reporting that the CXCR3 ligand CXCL9 is able to desensitize the response of memory T cells to the CXCR4 ligand CXCL12. As the authors suggest, heterologous chemokine receptor regulation represents a powerful regulatory mechanism for the control of inflammation. Using a previously described mimetic of CXCL10 (2, 3), another CXCR3 ligand, we demonstrated cross-regulation of CXCR4 and CCR5 in vitro and in vivo (4). The work of Giegold et al. (1) complements our study as although the three ligands of CXCR3 (CXCL9, CXCL10 and CXCL11) are able to elicit T cell migration, recent studies have suggested that these are allosteric ligands that elicit ligand-specific responses (5), which represent an additional level of potential regulation (6). Having described the internalization of CXCR4 and CCR5 upon CXCR3 ligation, we explored the mechanism underlying this and observed a chemokine receptor heterodimer of CXCR3 and CCR5 on the surface of T cells and demonstrated a PKC-dependent cross-phosphorylation of CCR5 by the CXCR3 ligand. Based on our study and the work of Giegold et al. (1), we therefore suggest that CXCR3 may also form a heterodimer while allowing similar cross-phosphorylation of CXCR4. This would suggest a mechanistic explanation for their observations of a loss of surface receptor and consequent chemokine responsiveness.

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We greatly appreciate the interest of O'Boyle et al. in our recent paper (1) and their contributions to the functional interaction of GPCR chemokine receptors (2). We definitely share the opinion that the interaction of chemokines, or in a broader perspective of GPCRs involved in migration, is of great importance to understand the pathophysiology of chronic inflammation and cancer, but also of physiological conditions like bone marrow cell homeostasis. In our lymphocyte experiments, we have no evidence so far for a CXCR3/CXCR4-heterodimer formation suggested by O'Boyle et al. However, recently Watts et al. investigated CXCR3/CXCR4-heterodimers in HEK293T cells (3). A small CXCR3 agonist, VUF10661, impaired binding of CXCL12 to CXCR4, a finding supporting O'Boyle's data. The effects are explained by an allosteric interaction of CXCR4 and CXCR3 upon agonist binding. Moreover, Watts et al. (3) demonstrated a specific β-arrestin2 recruitment to CXCR3/CXCR4-heteromers. Interestingly, the CXCR4/CXCR7 heterodimer complex also recruits β-arrestin, resulting in preferential activation of β-arrestin–linked signaling pathways and in enhanced cell migration (4). A further study with T lymphocytes, however, showed that CXCR7 can both enhance and decrease CXCL12-mediated chemotaxis (5). This indicates that, apart from heterodimer formation, the final biological effect of multiple chemokines acting through their cognate GPCRs is dependent on the specific cell-type and its respective differentiation status–dependent signaling apparatus. Adding complexity, the finding that the lipid mediator S1P via S1PR3 is directly altering the phosphorylation status of CXCR4 further extends the scope not only to another family of migratory active GPCRs but moreover to physiological conditions (6). Despite their therapeutic potential, the development of chemokine modulatory drugs has declined. We think that studies like the ones discussed in this correspondence are of decisive importance to better understand interactions of multiple chemotactic factors, which in a temporal and spatial order affect the distribution and final destination of immune cells, and thus may finally support new immunotherapeutic approaches.

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