



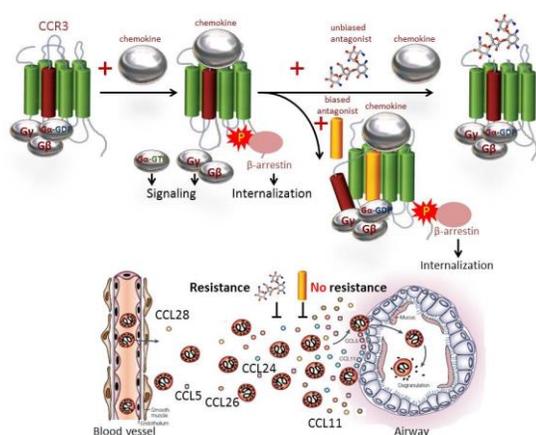
COLLOQUIUM
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DV 3130

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Biased Antagonism of GPCR Signaling: Overcoming Antagonist Tolerance



G protein-coupled receptors (GPCRs) are among the most important therapeutic targets in the human body. Although initially effective, many drugs targeting GPCRs lose their potency after prolonged administration. This phenomenon is called drug tolerance. Tolerance is frequently caused by drug-induced receptor internalization and recycling. These processes control the availability of the receptors for interaction with the drug or the natural ligands. How the receptor availability to interact with extracellular molecules is associated with drug tolerance can be exemplified by the action of GPCR antagonists. Antagonists are drugs that inhibit GPCR stimulation by its ligands. Antagonists can prevent receptor internalization. This causes the receptor to accumulate on the cell surface where it can be activated by

natural ligands. Eventually, the natural ligands overcome the inhibitory effects of the antagonists, leading to tolerance. We show that tolerance can be avoided by the use of biased antagonists, drugs that inhibit the undesirable function of G-proteins but do not inhibit receptor internalization. To investigate how biased antagonists avoid tolerance, we used GPCRs CXCR4 and CCR3 as examples. The CXCL12-CXCR4 chemokine-receptor pair regulates cell migration and stem cell homing to the bone marrow, but also promotes cancer metastasis. Therapeutic targeting of CXCR4 currently relies on a single antagonist, AMD3100. Due to rapidly developing tolerance, AMD3100 did not demonstrate expected efficiency in mobilization of leukemic blasts from the bone marrow in acute myeloid leukemia patients. CCR3 is expressed on eosinophils and can be stimulated by multiple chemokines. CCR3 mediated recruitment of eosinophils to the sites of inflammation is associated with many allergic inflammatory diseases. Therapeutic targeting of CCR3 with antagonists has been unsuccessful. Tolerance of CCR3 antagonists can be the problem. We found that peptides derived from the second transmembrane helices of CXCR4 and CCR3 act as biased antagonists. The peptides potently and selectively inhibit the function of G-proteins coupled to CXCR4 and CCR3 but permit receptor internalization. The peptides prevent receptor accumulation on the cell surface and retain their ability to inhibit chemotaxis after prolonged exposure.

Importantly, the CCR3 biased antagonist has shown efficacy in a mouse model of eosinophilic esophagitis. Thus, we have identified biased antagonists of CXCR4 and CCR3 that avoid the problem of tolerance associated with unbiased antagonists. This demonstrates the feasibility of using functionally selective drugs as anti-GPCR therapies to circumvent antagonist tolerance.