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Regulation of CXCR2 Expression and Function by a Disintegrin and metalloprotease-17 (ADAM17)

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Abstract

The chemokine receptor CXCR2 is expressed at high levels on circulating neutrophils and is critical for directing their migration to sites of inflammation. CXCR2 surface levels are rapidly modulated by 2 mechanisms-cell internalization and recycling upon ligand binding-and by a metalloprotease activity following overt neutrophil activation by nonligand stimuli. The latter process has only been described in human neutrophils, and essentially, nothing is known about its functional relevance and the specific protease involved. We show that targeting ADAM17 in mouse and human neutrophils blocks CXCR2 down-regulation induced by nonligand stimuli but not by chemokine ligands. This was determined by use of a selective ADAM17 inhibitor, an ADAM17 function-blocking antibody, and ADAM17 gene-targeted mice. CXCR2 is known to undergo a marked down-regulation during various inflammatory disorders, and this is associated with impaired neutrophil recruitment. We show that blocking ADAM17 activity reduced CXCR2 down-regulation on circulating neutrophils and enhanced their recruitment during acute inflammation, which was reversed by a CXCR2 inhibitor. Taken together, our findings demonstrate that unlike CXCR2 internalization, ADAM17 induction down-regulates the receptor in an irreversible manner and may serve as a master switch in controlling CXCR2 function, but may also contribute to neutrophil dysfunction during excessive inflammation.

Keywords: chemokines; inflammation; neutrophil.