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The AP-2 clathrin adaptor mediates endocytosis of an inhibitory killer cell Ig-like receptor in human NK cells

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Abstract

Copyright © 2014 by The American Association of Immunologists, Inc. All rights reserved. Stable surface expression of human inhibitory killer cell Ig-like receptors (KIRs) is critical for controlling NK cell function and maintaining NK cell tolerance toward normal MHC class I+ cells. Our recent experiments, however, have found that Ab-bound KIR3DL1 (3DL1) readily leaves the cell surface and undergoes endocytosis to early/recycling endosomes and subsequently to late endosomes. We found that 3DL1 internalization is at least partially mediated by an interaction between the μ2 subunit of the AP-2 clathrin adaptor complex and ITIM tyrosine residues in the cytoplasmic domain of 3DL1. Disruption of the 3DL1/μ2 interaction, either by mutation of the ITIM tyrosines in 3DL1 or mutation of μ2, significantly diminished endocytosis and increased surface expression of 3DL1 in human primary NK cells and cell lines. Furthermore, we found that the 3DL1/AP-2 interaction is diminished upon Ab engagement with the receptor, as compared with untreated cells. Thus, we have identified AP-2-mediated endocytosis as a mechanism regulating the surface levels of inhibitory KIRs through their ITIM domains. Based on our results, we propose a model in which nonengaged KIRs are internalized by this mechanism, whereas engagement with MHC class I ligand would diminish AP-2 binding, thereby prolonging stable receptor surface expression and promoting inhibitory function. Furthermore, this ITIM-mediated mechanism may similarly regulate the surface expression of other inhibitory immune receptors.

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