



Antibody Fc: Chapter 1. Antibody-Dependent Cellular Cytotoxicity (ADCC)

Victor Raúl Gómez Román, Joseph C. Murray, Louis M. Weiner

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Antibody-dependent cellular cytotoxicity (ADCC), also called antibody-dependent cell-mediated cytotoxicity, is an immune mechanism through which Fc receptor-bearing effector cells can recognize and kill antibody-coated target cells expressing tumor- or pathogen-derived antigens on their surface. Numerous associations between ADCC activity, Fc receptor polymorphisms, and clinical outcomes have been observed in both the settings of vaccination and monoclonal antibody therapy. Here, the effector cells and receptors involved in ADCC are introduced, followed by a description of the four main stages and mechanisms leading to the antibody-dependent effector-mediated killing of the target cell: (1) Recognition of the target cell and Fc receptor cross-linking on the surface of the effector cell; (2) phosphorylation of immunoreceptor tyrosine-based activation motifs (ITAMs) by cellular src kinases within the effector cell; (3) triggering of three main downstream signaling pathways in the effector cell, resulting in cytotoxic granule polarization and release; and (4) killing of the target cell via the predominant perforin/granzyme cell death pathway. Further, a summary and a discussion are presented in relation to case studies in which in vitro ADCC activity correlates with protection against infectious diseases and outcomes in monoclonal antibody therapy of cancer in vivo . The means by which these mechanisms are currently being exploited by recombinant antibody engineering, and a path toward a future in which designed vaccines take advantage of variant ADCC activity are also discussed. Throughout the chapter, attention is drawn to the fact that, while the majority of ADCC studies have been based on research using peripheral blood mononuclear cells in which NK cells have been assumed to be the main effectors, questions remain unanswered about ADCC mediated by non-NK cell populations in peripheral blood and in mucosal compartments.

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