Cytotoxic Mechanisms of Immunotherapy: Harnessing Effector Functions of anti-Tumor Monoclonal Antibodies

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Compelling evidence indicates that Type I CD20 mAbs rituximab and ofatumumab, which are used in the treatment of B cell malignancies, only kill tumor cells via immune effector functions, which require Fc recognition of cell-bound mAbs. The opsonized cells can be killed via antibody-dependent cell-mediated cytotoxicity or due to phagocytosis by effector cells; alternatively, the opsonized cells can bind C1q and activate complement, promoting C3b deposition followed by downstream lysis via the membrane attack complex. Our confocal microscopy studies have allowed us to generate movies of the cytotoxic reaction mediated by mAbs and complement, which is manifested by the rapid generation and release from the cell surface of long thin structures ("streamers", or tunneling nanotubules) that grow out of the cell surface. Moreover, we and others have found that saturation/exhaustion of effector killing mechanisms at high tumor burdens can severely compromise therapies. These findings may have profound and general implications for the use of mAbs in cancer immunotherapy.

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