IMMUNOLOGY

An unexpected complement

Depending on the context, the immune system can both promote and inhibit tumour growth. The complement system has been proposed to enhance the efficacy of anticancer monoclonal antibody therapy, but there has been little research into the potential tumour-promoting ability of complement. John Lambris and colleagues found this surprising, given the strong proinflammatory properties of complement effectors.

The authors tested their hypothesis that complement could promote tumour growth using the TC-1 syngeneic mouse model of cervical cancer in which tumours develop after subcutaneous injection of tumour cells. Immunofluorescence staining indicated that cleavage products of C3, the main protein of the complement activation cascade, were deposited along the tumour vasculature in tumour-bearing mice. Furthermore, tumour growth was impaired in *C3*-deficient mice.

There are three known pathways of complement activation (classical, lectin and alternative), all of which converge at C3. The authors assessed which pathway(s) was involved and found that tumour growth was impaired in mice lacking C4 (required for the classical and lectin pathways), but not in mice lacking complement factor B (required for the alternative pathway). C1q, which initiates the classical pathway, was found to be deposited along the tumour vasculature, indicating that the classical pathway is the main source of complement activation in TC-1 tumours.

C5a is a downstream component of the complement activation pathway, so the authors investigated its role in tumour growth. The peptidic C5a receptor (C5aR) antagonist impaired tumour growth in wild-type mice at a level comparable to that of paclitaxel treatment. Furthermore, the reduction in tumour volume was similar in *C5ar*-deficient mice.

How does C5a contribute to tumour growth? Because the genetic *C5ar* deficiency was in the host mouse and not the tumour cells, the authors concluded that C5a contributes to tumour growth primarily through effects on host cells. They found increased numbers of tumour-infiltrating $CD8^+$ T cells (which inhibit tumour growth) in mice treated with the C5aR antagonist, and depletion of $CD8^+$ T cells from *C5ar*-deficient mice accelerated tumour growth. The $CD8^+$ T-cell response to tumours is suppressed by myeloid-derived suppressor cells (MDSCs), and the authors showed that the recruitment of MDSCs to tumours depends on C5a signalling through C5aR in MDSCs. MDSCs inhibit $CD8^+$ T cells by production of reactive oxygen and nitrogen species (ROS and RNS), the overall levels of which were reduced in MDSCs from *C5ar*-deficient mice. Further studies showed that C5a increases ROS and RNS in the tumour microenvironment by two mechanisms: recruitment of one subpopulation of MDSCs that intrinsically produce high levels of ROS and RNS, and enhancement of ROS and RNS production by another subpopulation.

These data suggest an unexpected role for the complement system in augmenting tumour growth. Although further studies are required to extrapolate these results to other tumour models and humans, inhibition of C5aR could be a valid therapeutic strategy.

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