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TUMOUR IMMUNOLOGY

Regulating MDSC recruitment

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of immune cells that accumulates in tumour-bearing hosts and in response to inflammation. Although it has been established that the capacity of MDSCs to inhibit T-cell responses prevents tumour rejection, the mechanisms that underlie MDSC accumulation and suppressor function are unclear. Now, two groups have shown that pro-inflammatory S100 proteins are crucial for MDSC accumulation, providing new clues on how inflammation and cancer might be linked.

Cheng *et al.* show that the levels of S100A9 and its dimerization partner, S100A8, were higher in mice with colon cancer than in tumour-free mice, and that the expression of these proteins correlated with MDSC accumulation in the same tissues. The findings that MDSC accumulation did not occur in S100A9-deficient mice and that transgenic overexpression of S100A9 promoted the accumulation of these cells indicate that this protein is essential for the recruitment of MDSCs. Furthermore, S100A9-deficient mice had T cells with greater tumour-specific cytolytic activity and showed higher rates of tumour rejection than wild-type mice, which supports the idea that preventing MDSC accumulation is an effective strategy to promote tumour rejection.

In a second study, Sinha *et al.* show that MDSCs from both healthy and tumour-bearing mice expressed S100 proteins as well as the molecules that act as S100 receptors, indicating that an autocrine loop might promote MDSC accumulation in tumours and at sites of inflammation. Administration of an antibody that is specific for the receptor of the S100A8–S100A9 heterodimer was used to show that preventing this receptor–ligand interaction reduced MDSC accumulation in mice with progressive mammary tumours.

But what induces the expression of S100 proteins, and how do they influence MDSC function at sites where these cells accumulate? Cheng *et al.* used several approaches to show that *S100a8* and *S100a9* are activated by STAT3 (signal transducer and activator of transcription 3), a protein that has previously been found to be hyperactivated in innate immune cells in tumour-bearing hosts. The authors also provide evidence that S100A9 is involved in the production of reactive oxygen species by the NADPH oxidase complex, the alteration of which might influence the differentiation of MDSCs. The results of Sinha *et al.* show that the binding of soluble S100 proteins to molecules on the surface of MDSCs led to activation of the nuclear factor-κB inflammatory signalling pathway. However, blocking the interaction between the S100A8–S100A9 heterodimer and its receptor *in vivo* was not found to alter the suppressive activity of MDSCs when they were isolated and assayed *in vitro*. This indicates that the main role of S100 proteins might be in the recruitment, rather than in the function, of MDSCs.

Although many unanswered questions remain, these studies suggest that S100 proteins are important for the accumulation of MDSCs in the context of cancer, in which they might serve as a useful therapeutic target to reduce tumour-induced immunosuppression. This link between inflammation, which induces both S100A8–S100A9 production and MDSC accumulation, and immunosuppression also provides a means by which inflammation can contribute to cancer.

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ORIGINAL RESEARCH PAPERS Cheng, P. *et al.* Inhibition of dendritic cell differentiation and accumulation of myeloid-derived suppressor cells in cancer is regulated by S100A9 protein. *J. Exp. Med.* 22 September 2008 (doi:10.1084/jem.20080132) | Sinha, P. *et al.* Proinflammatory S100 proteins regulate the accumulation of myeloid-derived suppressor cells. *J. Immunol.* **181**, 4666–4675 (2008)