TUMOUR IMMUNOLOGY

MDSCs come at a cost

Pregnancy is associated with general immune suppression. Interestingly, breast tumours that develop during or shortly after pregnancy are more aggressive. A recent study by Mauti *et al.* provides a link between these two observations by showing that the numbers and suppressive activity of myeloid-derived suppressor cells (MDSCs) increase during pregnancy. This results in reduced natural killer (NK) cell cytotoxicity and thereby contributes to increased tumour growth and metastatic permissiveness.

The authors observed that injection of pregnant mice with tumour cells of various origins (melanoma, fibrosarcoma, lymphoma and mammary carcinoma cells) resulted in increased tumour growth and metastasis compared with the tumour dissemination in control mice following tumour cell injection. While researching the mechanisms involved in increased tumour dissemination during pregnancy, they found that serum or plasma from pregnant mice did not affect tumour cell proliferation, excluding a role for pregnancy-related factors, such as hormones.

In vivo imaging studies in NOD-*scid* mice (which lack an adaptive immune system) revealed that non-pregnant mice started to clear tumour cells 6 hours after injection, and tumour cells were not detectable by day 4, whereas they persisted in pregnant mice. This indicated that increased tumour aggressiveness in pregnant mice may rely on defective innate immune cell functions. Further analysis showed that the percentages of NK cells in the blood and spleen, as well as their cytotoxic activity, were low in pregnant NOD-*scid* mice. Moreover, tumour load in pregnant mice was comparable to that in NK cell-deficient NOD-*scid* mice and in wild-type mice with NK cell-resistant tumours.

So, how is NK cell cytotoxicity regulated during pregnancy? Gene expression analysis of organs commonly associated with tumour metastasis revealed that genes associated with a pre-metastatic niche were upregulated in pregnant mice. Some of these genes are required for the recruitment of myeloid cells, and this led the authors to investigate the involvement of MDSCs, which are known to correlate with cancer stage. The percentages of MDSCs in the blood, spleen, lung and liver were significantly increased during pregnancy and the decrease in NK cell numbers followed the same kinetics. Moreover, MDSCs derived from pregnant mice suppressed NK cell cytotoxicity more efficiently than control mouse-derived MDSCs. Finally, antibody-mediated MDSC depletion prior to tumour cell injection resulted in reduced lung metastasis during pregnancy, whereas adoptive transfer of MDSCs from pregnant donors to control mice resulted in increased metastasis.

So, the numbers and suppressive activity of MDSCs increase not only in tumour-bearing mice and patients with cancer but also in pregnant mice, and this correlates with increased tumour growth and metastasis during pregnancy. The authors suggest that comparative studies of the tissue microenvironment in organs from pregnant mice and tumour-bearing mice may provide further insight into the immune cells and other factors that contribute to a pre-metastatic niche.

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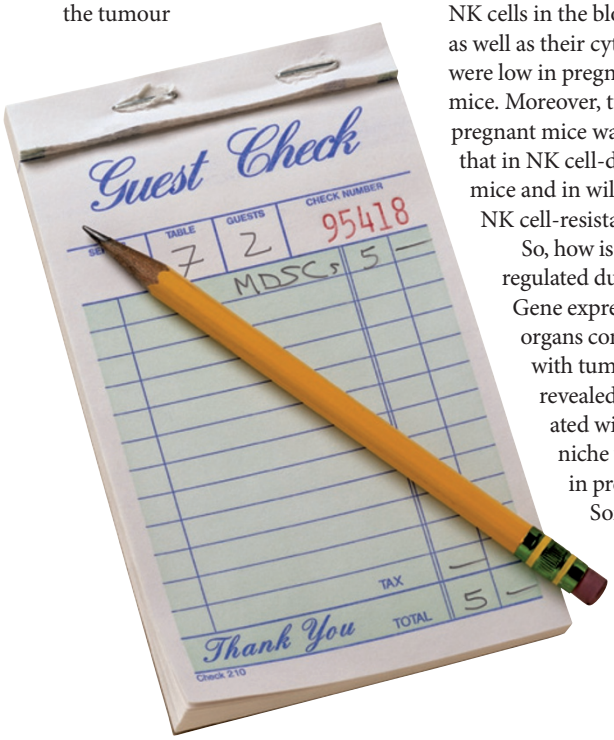

ORIGINAL RESEARCH PAPER Mauti, L. A. *et al.* Myeloid-derived suppressor cells are implicated in regulating permissiveness for tumor metastasis during mouse gestation. *J. Clin. Invest.* 6 Jun 2011 (doi:10.1172/JCI41936)

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