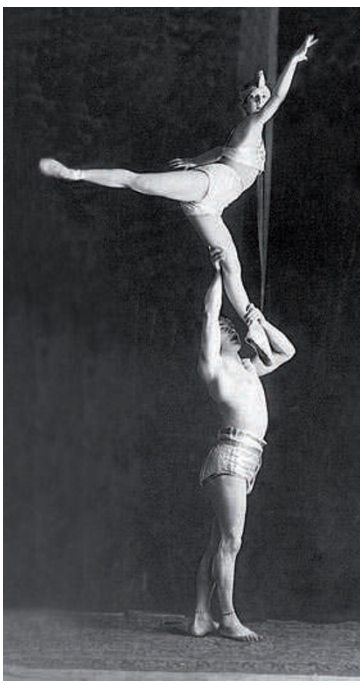
TUMOUR IMMUNOLOGY

# Antibodies lend support to tumours

This study explains how B cells can contribute to cancer development. It shows that antibodies, by engaging activating Fc receptors for IgG (FcγRs) on myeloid cells in premalignant lesions, favour the generation of a chronic inflammatory environment that promotes carcinogenesis.

The authors identified a role for humoral immunity in cancer development using a mouse model of skin cancer, in which expression of early region genes from human papilloma virus type 16 (HPV-16) in the skin causes epidermal hyperplasias that progress to malignant squamous cell carcinomas. HPV-16 mice that lacked mature B cells had decreased features of cancer progression, showing less leukocyte infiltration, angiogenesis and keratinocyte hyperproliferation than normal HPV-16 mice. In addition, HPV-16-specific antibodies, as well as various autoantibodies, were found at high titres in neoplastic skin of HPV-16 mice, and intradermal injection of these antibodies into syngeneic wild-type mice promoted leukocyte recruitment to the skin.



So, how might antibodies contribute to the generation of a cancer-promoting inflammatory environment? Analysis of cells infiltrating premalignant skin in HPV-16 mice indicated that mast cells and immature and mature myeloid cells express several activating FcγRs, which are known to trigger various inflammatory leukocyte effector functions following antibody binding. HPV-16 mice lacking FcRγ (the crucial signalling adaptor for activating FcγRs) had decreased inflammatory cell infiltration, angiogenesis, keratinocyte hyperproliferation and incidence of squamous cell carcinomas, similar to B cell-deficient HPV-16 mice, supporting a role for these receptors in cancer progression. FcγRIII$^+$ mast cells were found to be a key cell population contributing to the pro-angiogenic and pro-tumorigenic environment; antibody-activated FcγRIII$^+$ mast cells produced vascular endothelial growth factor and promoted vascular endothelial cell and leukocyte migration *in vitro*.

The authors also found that the expression of activating FcγRs alters the phenotype of cell populations in neoplastic skin: the phenotypes of FcRγ-deficient dendritic cells and macrophages from HPV-16 mice were skewed towards an antitumour type 1 and an M1 type, respectively. Support that this polarized phenotype contributes to the lower cancer progression observed in FcRγ-deficient HPV-16 mice was provided by the finding that increased expression of CXC-chemokine ligand 10 by the FcRγ-deficient M1-type macrophages in neoplastic skin inhibited angiogenic properties of vascular cells *in vitro*.

So, antibody binding to activating FcγRs promotes the generation of a pro-tumour environment in premalignant tissue that directs the recruitment, composition, phenotype and effector function of inflammatory leukocytes, which drive neoplastic progression and carcinoma development. Interruption of this cascade by therapeutic targeting of B cells or FcRγ signalling pathways may hold promise for limiting cancer progression.

*Lucy Bird*

**ORIGINAL RESEARCH PAPER** Andreu, P. *et al.* FcRγ activation regulates inflammation-associated squamous carcinogenesis. *Cancer Cell* 4 Feb 2010 (doi:10.1016/j.ccr.2009.12.019)