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TUMOUR IMMUNOLOGY

Differing roles for MYD88 in carcinogenesis

MYD88 — an adaptor molecule involved in Toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) signalling — has been implicated in tumorigenesis through pro-inflammatory mechanisms. Now, two papers in the *Journal of Experimental Medicine* show how signalling through MYD88 contributes to skin and pancreatic carcinogenesis in distinct ways.

When Cataisson *et al.* observed that expression of MYD88 in both bone marrow-derived cells and keratinocytes was required for skin carcinogenesis in a mouse model of tumour formation, they decided to investigate the contribution of MYD88 to the RAS-transformed keratinocyte phenotype. They found that signalling through IL-1R–MYD88 was needed to activate nuclear factor-κB (NF-κB)-regulated expression of pro-tumorigenic factors — such as CXC-chemokine ligand 1 (CXCL1) and tumour necrosis factor (TNF) — in RAS-transformed keratinocytes. When the researchers blocked IL-1 signalling in the keratinocytes, they observed upregulation of several genes associated with keratinocyte differentiation, as well as the expected downregulation of cytokine and chemokine genes. The authors suggest that oncogenic RAS signalling causes the release of IL-1α, triggering activation of IL-1R–MYD88 signalling. This in turn leads to NF-κB transcriptional activity, which causes the altered differentiation of keratinocytes that is characteristic of their transformed phenotype, as well as other pro-inflammatory effects.

Cataisson *et al.* also found that although RAS-transformed keratinocytes from *Myd88*-knockout mice showed only minimal tumour growth when grafted to mice with competent MYD88 expression, keratinocytes from IL-1R-deficient or wild-type mice produced substantial tumours in graft recipients. This suggests that the activation of MYD88 during tumorigenesis is not solely driven by IL-1R signalling, and the authors propose that other members of the TLR and IL-1R superfamily may contribute.

Ochi and colleagues focused on the role of TLR4 signalling in inflammatory cells in regulating pancreatic carcinogenesis. Using a mouse model in which expression of $KRAS^{G12D}$ (an oncogenic mutant form of RAS) is targeted to pancreatic cells, they found that blocking the MYD88-independent TRIF pathway that is downstream of TLR4 protected against pancreatic tumour formation. By contrast, blocking the MYD88-dependent pathway surprisingly increased pancreatic inflammation and malignant progression. Unlike in the skin cancer study by Cataisson *et al.*, Ochi and colleagues found that the effects of MYD88 inhibition were mediated solely by bone marrow-derived inflammatory cells and that pancreatic epithelial cells did not contribute to the malignant phenotype that arose owing to MYD88 inhibition.

Ochi *et al.* went on to show that dendritic cells mediate the effects of MYD88 inhibition by inducing T cell differentiation towards a T helper 2 (T_H2) cell phenotype. $CD4^+$ T cell depletion rescued *Myd88*$^{-/-}$ mice but not wild-type mice from pancreatic inflammation and tumorigenesis. They found that the T_H2 cells that differentiated during MYD88 inhibition were specific for pancreatic antigens, suggesting that dendritic cells capture antigens from the injured pancreas and present them to naive T cells to promote the generation of antigen-specific effector T cells that drive inflammation and neoplastic transformation.

Both papers indicate central roles for MYD88 signalling in carcinogenesis, but the findings also highlight the complexity of the inflammatory response in carcinogenesis.

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ORIGINAL RESEARCH PAPERS Cataisson, C. *et al.* IL-1R–MyD88 signaling in keratinocyte transformation and carcinogenesis. *J. Exp. Med.* **209**, 1689–1702 (2012) | Ochi, A. *et al.* MyD88 inhibition amplifies dendritic cell capacity to promote pancreatic carcinogenesis via Th2 cells. *J. Exp. Med.* **209**, 1671–1689 (2012)

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