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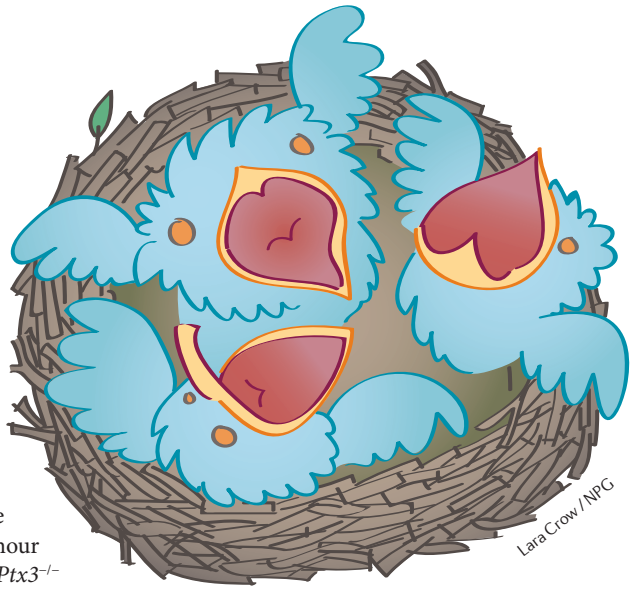

Lara Crow / NPG

INFLAMMATION

An innate response

Inflammation is a promoter of tumour development and progression, so identifying the components of an inflammatory response that contribute to this is important. Alberto Mantovani and colleagues have found that loss of a regulator of the complement cascade, pentraxin 3 (PTX3), accelerates tumour development in mice owing to a complement- and macrophage-mediated immune response.

Using two different carcinogens, which result in either skin tumours or sarcomas in mice, Mantovani and colleagues found that *Ptx3*-knockout mice ($Ptx3^{-/-}$) developed more tumours that grew more aggressively compared to *Ptx3* wild-type mice ($Ptx3^{+/+}$). Serum levels of PTX3 were increased after treatment of $Ptx3^{+/+}$ mice with the sarcoma inducing carcinogen 3-methylcholanthrene (3-MCA), and immunohistochemistry of established sarcomas indicated that PTX3 is expressed by blood vessels, macrophages, neutrophils and interstitial stromal cells, but not by the sarcoma cells. In addition, bone marrow chimeric mice ($Ptx3^{+/+}$ mice receiving $Ptx3^{-/-}$ bone marrow and vice versa) showed that PTX3 is expressed in the tumours by both haematopoietic and non-haematopoietic cells.

PTX3 has no effect on cell proliferation, but it can interact with Fcγ receptors (expressed by innate immune cells, such as macrophages) and has antibody-like properties that are associated with the regulation of an inflammatory response. Analyses of established sarcomas indicated increased levels of macrophages and monocytes in $Ptx3^{-/-}$ sarcomas, but similar levels of T cells in $Ptx3^{-/-}$ and $Ptx3^{+/+}$ sarcomas. Levels of pro-inflammatory cytokines, such as tumour necrosis factor (TNF), interleukin-1β (IL-1β), IL-6, chemokine CC motif ligand 2 (CCL2) and vascular endothelial growth factor (VEGF), were increased in the tumour homogenates from $Ptx3^{-/-}$ mice, and systemic levels of VEGF and TNF were also increased. CCL2 is involved in monocyte chemotaxis, and treatment of $Ptx3^{-/-}$ mice with an anti-CCL2 antibody reduced the levels of 3-MCA induced sarcomas to those evident in wild-type mice.

As PTX3 is also involved in the regulation of the complement cascade and interacts with complement control proteins, such as factor H, the authors examined the levels of active complement in sarcomas from both genetic backgrounds. Increased deposition of the complement components C3 and C5a was evident in $Ptx3^{-/-}$ compared with $Ptx3^{+/+}$ sarcomas. Correspondingly, C3-deficent mice and $Ptx3^{-/-}$ mice treated with a C5a inhibitor had reduced incidences and growth rates of 3-MCA induced sarcomas. Additional experiments indicated that $Ptx3^{-/-}$ sarcomas had reduced the levels of factor H. Together, these data indicate that loss of PTX3 leads to an increased complement-mediated inflammatory response that is associated with a lack of factor H.

Inflammation has been associated with genomic instability in tumorigenesis, so the authors looked at *Trp53* and *Kras* mutation rates in the sarcomas. *Trp53* was mutated more often in sarcomas from $Ptx3^{-/-}$ mice, but there was no difference in the mutation rate of *Kras*. Levels of the modified base 8-OH-deoxyguanosine were also increased in sarcomas from $Ptx3^{-/-}$ mice, as were other markers of DNA damage, such as 53BP1. The authors conclude that the increased inflammation that results from PTX3 loss can induce genetic instability.

When analysing human tumours, the authors found that the *PTX3* promoter is hypermethylated in samples of colorectal cancer, squamous cell skin carcinoma and leiomyosarcomas, and *in silico* analyses indicated increased levels of *PTX3* methylation in colorectal cancer samples. In agreement with these findings, treatment of colorectal cancer cell lines in which *PTX3* is methylated with a demethylating agent resulted in PTX3 mRNA and protein expression, and increased chromatin markers associated with active gene transcription.

These data indicate that, in mice, PTX3 is an important regulator of the innate immune response to carcinogens, and that its loss increases both a complement-mediated and a macrophage-sustained immune response that promotes tumour development.

> “Analyses of established sarcomas indicated increased levels of macrophages and monocytes in $Ptx3^{-/-}$ mice”

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The author declares no competing interests.

ORIGINAL RESEARCH PAPER Bonavita, E. *et al.* PTX3 is an extrinsic oncosuppressor regulating complement-dependent inflammation in cancer. *Cell* **160**, 700–714 (2015)