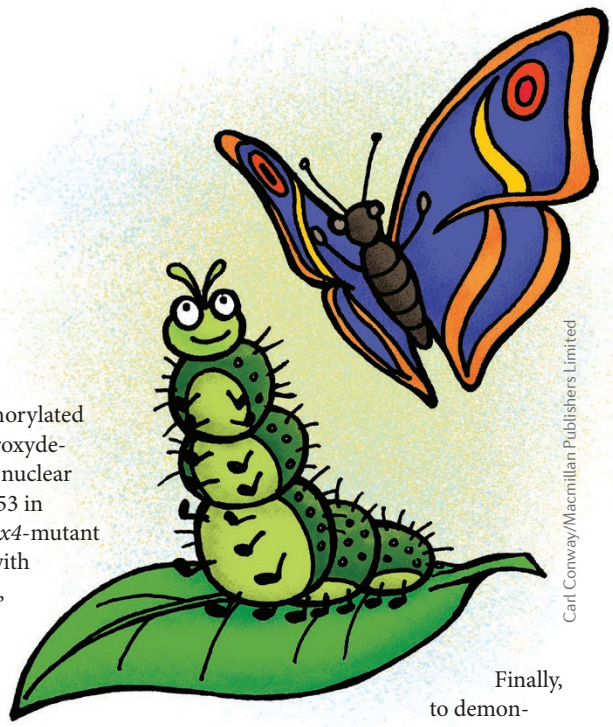
Nature Reviews Cancer | Published online 25 Jan 2018; doi:10.1038/nrc.2018.4



Carl Conway/Macmillan Publishers Limited

TUMOUR MICROENVIRONMENT

Radical changes

It has been hypothesized that increased production of reactive oxygen species (ROS) from inflammatory cells, as observed during chronic inflammation, triggers DNA damage and mutations. Yet, there has been no direct evidence in vivo showing that individual cell types in the tumour microenvironment can induce mutations in neighbouring epithelial cells via ROS. A study now published in *Cancer Cell* has revealed that elevated ROS production in myeloid cells can initiate intestinal tumour growth and stimulate tumour progression, providing a potential explanation for the increased cancer risk in patients with inflammatory diseases.

To demonstrate the effects of constitutively increased ROS production in myeloid cells during tumour development in vivo, Canli et al. generated mice with a myeloid cell-specific deletion of the gene encoding glutathione peroxidase 4 (GPX4), an antioxidant that scavenges ROS, leading to increased intracellular ROS levels specifically in macrophages and neutrophils, without inducing substantial myeloid cell death.

Unexpectedly, inducing intestinal tumorigenesis with the carcinogen azoxymethane (AOM) in *Gpx4*-mutant mice did not change tumour incidence or tumour size when compared with control mice. However, invasive tumour growth, not normally stimulated in wild-type mice treated with AOM, was observed in AOM-treated, *Gpx4*-deficient mice but not in control mice. Looking for evidence of increased oxidative DNA damage, the authors noted increased labelling of phosphorylated H2A.X and 8-hydroxydeoxyguanosine and nuclear accumulation of p53 in tumour cells of *Gpx4*-mutant mice. Consistent with these observations, whole-exome sequencing showed an increased mutational load in tumours from *Gpx4*-deficient mice compared with those of control mice, including an increased frequency of mutations in genes associated with an invasive colorectal cancer phenotype.

> “elevated ROS production in myeloid cells can initiate intestinal tumour growth and stimulate tumour progression”

Further mechanistic studies revealed that the induced DNA damage was independent of signalling through tumour necrosis factor receptor 1 (TNFR1) in epithelial cells. However, an autocrine TNFα loop involving IκB kinase-β (IKKβ) and AKT signalling was required for the infiltration of myeloid cells and consequent tumour invasion. To ascertain how myeloid cells could indirectly induce DNA damage by increasing oxidative stress in epithelial cells in vivo, the authors crossed *Gpx4*-deficient mice with transgenic mice expressing a modified mitochondrial-localized catalase, an enzyme that catalyses the decomposition of hydrogen peroxide (H_2O_2) selectively in intestinal epithelial cells. Expression of this enzyme rescued AOM-treated, *Gpx4*-deficient mice from forming invasive tumours and reduced the DNA damage in tumour cells.

Finally, to demonstrate that increased ROS secretion from myeloid cells during chronic inflammation was sufficient to initiate tumorigenesis without exposure to a carcinogen, Canli et al. challenged *Gpx4*-mutant mice with dextran sodium sulfate (DSS) to induce colitis. Four rounds of treatment led to the development of at least one colonic adenoma in *Gpx4*-mutant mice whilst tumours were absent from wild-type mice. Interestingly, deletion of *Gpx4* from myeloid cells alone without chronic inflammation caused tumours to form in 70% of mice by 27 months of age (which were largely found in the lungs) compared with spontaneous tumour development in only 30% of wild-type mice.

Future studies will need to reconcile how ROS production can be targeted to inhibit intestinal tumour progression given that in other systems, elevated ROS has been observed to induce senescence and apoptosis in tumour cells.

Anna Dart

ORIGINAL ARTICLE Canli, Ö. et al. Myeloid cell-derived reactive oxygen species induce epithelial mutagenesis. *Cancer Cell* **32**, 869–883 (2017)