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IN BRIEF

LEUKAEMIA

The real deal

Although vascular density and vascular endothelial growth factor (VEGF) levels are increased in acute myeloid leukaemia (AML), anti-VEGF therapy has been ineffective in clinical trials. Mainly studied *in vitro*, the crosstalk between leukaemic cells and endothelial cells (ECs) remains poorly understood. Using two-photon microscopy, a new study has investigated the bone marrow vasculature in AML *in vivo*. Engraftment of patient-derived AML cells into mice increased vascular permeability compared with control mice engrafted with normal human haematopoietic stem and/or progenitor cells, an effect that persisted after treatment with the AML chemotherapy cytarabine. Interestingly, the NAPDH oxidase *Nox4* was the most upregulated common gene in bone marrow-derived ECs of AML-engrafted mice, and was associated with high production of reactive oxygen species in the bone marrow as well as induction of nitric oxide (NO) synthase 3 (NOS3) in ECs. Accordingly, levels of NO, an inducer of vascular permeability, in the bone marrow of AML-engrafted mice were increased compared with control mice. Pharmacological NOS inhibition in combination with cytarabine-reduced AML progression and vascular permeability in the mice, providing evidence for a potential clinical benefit of targeting NOS in the bone marrow vascular niche in AML.

ORIGINAL ARTICLE Passaro, D. *et al.* Increased vascular permeability in the bone marrow microenvironment contributes to disease progression and drug response in acute myeloid leukemia. *Cancer Cell* **32**, 324–341 (2017)

CELL DEATH

A better way to die

Inducing apoptosis has long been considered an important effector mechanism of many anti-cancer therapies. Yet, several studies have suggested that engaging apoptosis can have tumour-promoting effects. During apoptosis, mitochondrial outer membrane permeabilization can lead to caspase activation. However, caspase activity can have undesirable outcomes, such as DNA damage. In search of a better way to eliminate cancer cells, Giampazolias *et al.* demonstrated that under caspase-deficient conditions, mitochondrial outer membrane permeabilization can trigger tumour necrosis factor (TNF)-dependent necroptosis, a type of caspase-independent cell death. In contrast to apoptosis, cells undergoing caspase-independent cell death generated a pro-inflammatory and immunogenic anti-tumour response through the activation of nuclear factor-κB (NF-κB). Specifically, this anti-tumour immune response, stimulated by caspase-independent cell death, involved tumour infiltration of T cells and activation of macrophages. Furthermore, and most importantly, engagement of caspase-independent cell death often led to complete tumour regression in the presence of an intact immune system in syngeneic colorectal cancer mouse models. Overall, this study highlights the potential value of inducing caspase-independent cell death as a more efficient means of treating cancer.

ORIGINAL ARTICLE Giampazolias, E. *et al.* Mitochondrial permeabilization engages NF-κB-dependent anti-tumour activity under caspase deficiency. *Nat. Cell Biol.* **19**, 1116–1129 (2017)

FURTHER READING Ichim, G. and Tait, S. W. G. A fate worse than death: apoptosis as an oncogenic process. *Nat. Rev. Cancer* **16**, 539–548 (2016)