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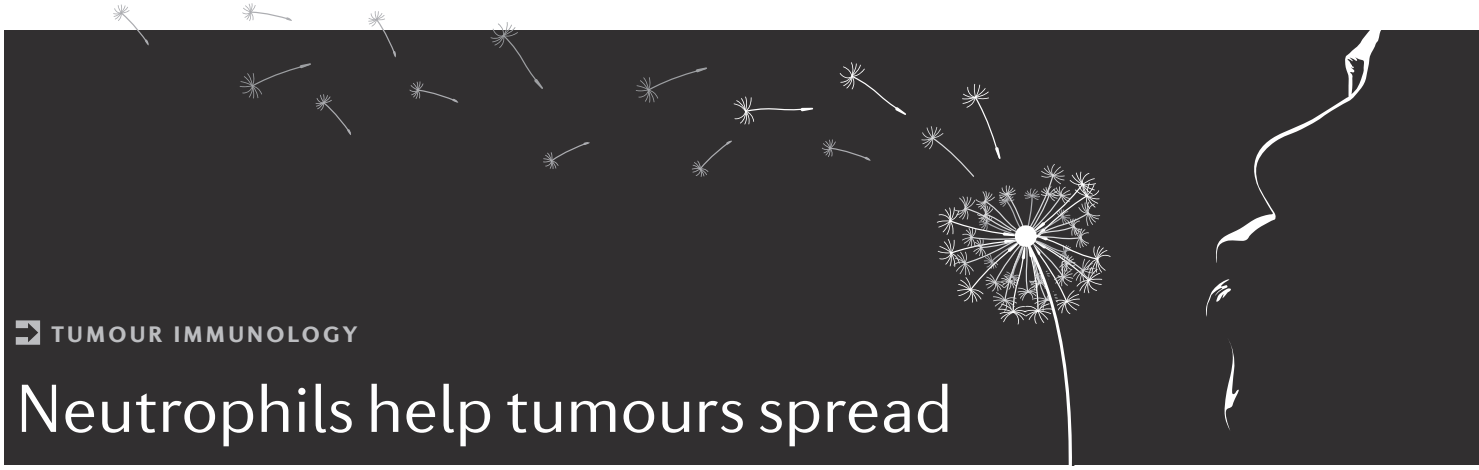

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TUMOUR IMMUNOLOGY

# Neutrophils help tumours spread

Cancer cells in a tumour are heterogeneous and have different tumorigenic potential. The ability of cancer cells to seed a distant site is thought to depend on previous changes in the composition of leukocytes that favour metastatic growth. A new study published in *Nature* shows that neutrophils drive the metastatic spread of breast cancer cells to the lungs through the release of leukotrienes.

Wculek and Malanchi studied the pro-metastatic environment in a mouse mammary tumour virus–polyoma middle T antigen (MMTV–PyMT) metastatic lung cancer model, in which cancer cells that have a higher metastasis-initiation ability can be measured by expression of CD24 and CD90. Notably, tumour-bearing mice showed an accumulation of neutrophils in pre-metastatic lungs and also during metastatic progression, although the number of neutrophils in the primary tumour remained low. The relevance of this accumulation to metastatic progression was confirmed in mice that were neutropenic (owing to genetic deficiency of granulocyte colony-stimulating factor). Neutropenic tumour-bearing mice had a marked reduction in spontaneous lung metastasis compared with control mice, despite no differences in primary tumour growth. Similarly, fewer cancer cells colonized the lungs when neutrophils were depleted using LY6G-specific antibody just before metastatic dissemination.

> “fewer cancer cells colonized the lungs when neutrophils were depleted”

Next, the authors sought to determine the potential effect of neutrophil-secreted factors on tumour cells. The exposure of tumour cells to conditioned medium from cultures of pre-metastatic lung neutrophils led to increased sphere-formation ability *in vitro* and enhanced metastatic initiation potential *in vivo*. Indeed, the number of highly metastatic $CD24^{+}CD90^{+}$ cells doubled if cancer cells seeded in the lungs were exposed to neutrophil-conditioned media. This effect was found to be mediated by the lipids leukotriene $B_4$ ($LTB_4$) and cysteinyl leukotrienes $LTC_4$, $LTD_4$ and $LTE_4$, which are products of the enzyme arachidonate 5-lipoxygenase (ALOX5) and were found at high levels in the lung neutrophil cultures. Accordingly, leukotriene receptor expression was associated with highly metastatic cells, and treatment with leukotrienes specifically increased the proliferation of this subpopulation of tumour cells, suggesting that neutrophil-derived leukotrienes provide a selective proliferative advantage to cancer cells with intrinsically higher tumorigenicity.

The functional relevance of leukotrienes in metastasis *in vivo* was supported by the observation that inhibition of leukotriene synthesis by treatment of tumour-bearing mice with an ALOX5-specific inhibitor reduced spontaneous metastasis without altering primary tumours or lung neutrophil numbers. Metastatic cancer cells that did enter the lungs of treated mice showed very little proliferation.

So, in summary, this study identifies a pro-metastatic role for leukotriene-producing neutrophils and potentially a new target for future cancer therapeutics.

*Lucy Bird*

**ORIGINAL ARTICLE** Wculek, S. K. & Malanchi, I. Neutrophils support lung colonization of metastasis-initiating breast cancer cells. *Nature* **17**, 57–64 (2015)