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INSIGHTS

Neutrophil: A mobile fertilizer

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In this issue of *JEM*, Lee et al. (https://doi.org/10.1084/jem.20181170) provide evidence to show that early influx of neutrophils into omentum represents a key mechanism in establishing the premetastatic niche for the subsequent implantation of ovarian cancer cells at this site.

The study of cancer metastasis has been largely based on the "seed and soil" concept proposed by Stephen Paget in the late 1800s, in which he proposed that metastases can only be established when the tumor cell (seed) and specific tissue microenvironment (soil) are compatible (Paget, 1889). While it is well accepted that ovarian cancer metastasis has a strong tropism toward the omentum, the mechanisms involved in guiding the migration and implantation of ovarian tumor cells to this site are still poorly defined. Several studies have shown that the cross-talk between tumor cells and host myeloid cells modulates the formation of the premetastatic niche to favor subsequent tumor cell implantation (Sionov et al., 2015). Of note, a previous study showed that neutrophil accumulation in the lung occurred before the arrival of cancer cells in a mouse breast cancer model (Granot et al., 2011), suggesting that neutrophils can be a key cellular component for establishing the premetastatic niche. However, it is still unclear how neutrophils are mobilized to the premetastatic site and how these cells establish the premetastatic niche to be more "fertile" for the seeding of circulating cancer cells.

In this study by Lee et al., to identify the cellular components that promote the tropism of ovarian cancer cells for the omentum, the authors have investigated several ovarian cancer murine models. From this set of experiments, Lee et al. (2018) demonstrate that early accumulation of neutrophils close to the PNAd$^+$ vessels (presumably high endothelial venules [HEVs]) in the omentum represents a key step in forming the premetastatic niche for the subsequent implantation of ovarian cancer cells. A previous study showed that inhibition of HEV-mediated neutrophil recruitment to the omentum exacerbates septic peritonitis (Buscher et al., 2016). Together, these results demonstrate that neutrophil recruitment to the omentum may be relevant to inflammatory and malignant disorders. Neutrophils represent the frontline defenders against sterile and pathogenic insults. One major characteristic of neutrophils is that they are highly dynamic since they are among the first responders to be recruited to the inflamed/infected site. While it is well recognized that these cells are essential for the elimination of foreign microorganisms and the initiation of the tissue remodeling process, emerging data also suggest that neutrophils play a key role in different aspects of cancer pathogenesis. Notably, most of the studies looking at neutrophil–cancer interactions have focused on tumor-associated neutrophils at the primary tumor site, which are known to exert either pro- or antitumoral function depending on the tumor niche microenvironment. For instance, a seminal study from Fridlender et al. (2009) showed that blockade of TGF-β promotes the recruitment of neutrophils with increased antitumorigenic cytotoxicity and secreting CD8 T cell–attracting factors. On the other hand, neutrophils recruited to the tumor site have also been shown to elicit protumoral activities such as angiogenesis (Nozawa et al., 2006) and immune suppression (Schmielau and Finn, 2001; Youn et al., 2008). Taken together, these results suggest that neutrophil function in cancer is complex and highly context dependent.

Interestingly, as reported by Lee et al. (2018), there is no significant increase in circulating neutrophil numbers during the premetastatic stage, which is in contrast to neutrophilia often observed in both cancer patients and experimental mouse models of cancer (Sionov et al., 2015). Thus, this observation indicates that the recruitment of neutrophils to the premetastatic omental niche is not a passive process due to the overall increase of circulating neutrophil numbers, but instead is an active process. The bone marrow is the predominant physiological hematopoiesis site in adults (medullary). However, during immune responses, the spleen can serve as an extramedullary hematopoiesis site, which can continuously supply extra myeloid cells to meet the demand for these cells in chronic inflammation (Swirski et al., 2009). In the context of tumor, it has been reported that the spleen can act as a unique reservoir site for neutrophils and supplies additional cells during tumor progression (Cortez-Retamozo et al., 2012). An interesting question to address will be to determine the origin of the neutro-

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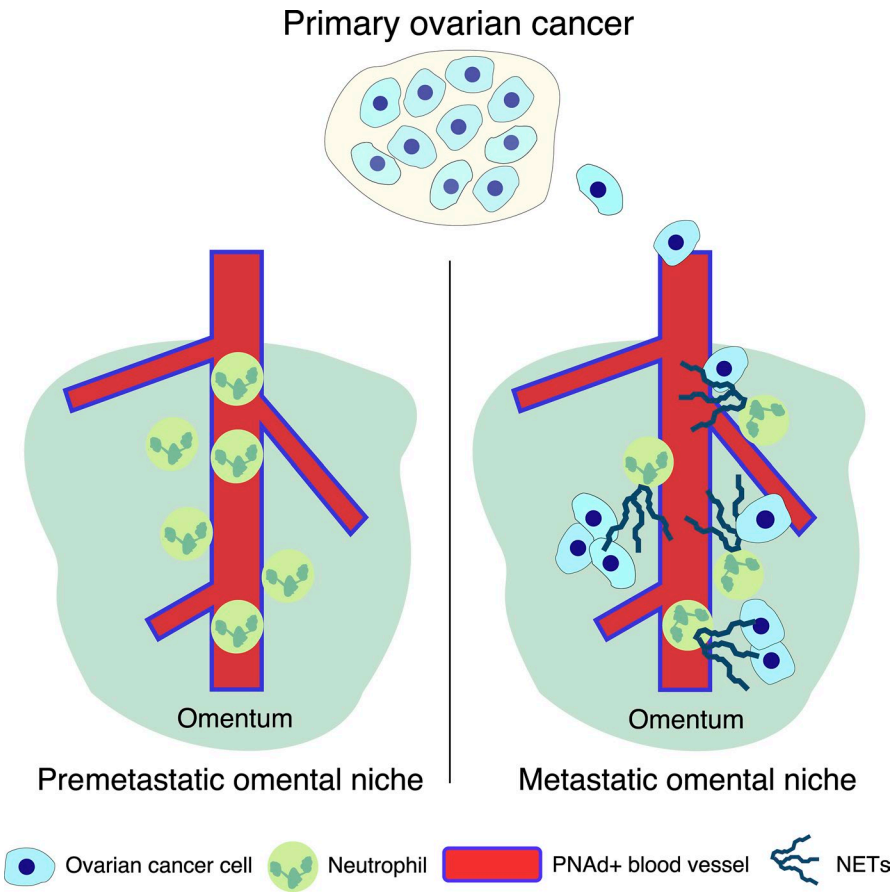

Primary ovarian cancer induces the formation of the premetastatic niche by mobilizing neutrophils to the omentum through the PNAd$^+$ blood vessels before the appearance of cancer cells. In response to cancer-derived factors, neutrophils are activated and release NETs. Consequently, these NETs promote dissemination of ovarian cancer cells to the omentum by trapping them at this site.

phils that are recruited to the premetastatic niche. Are these cells mobilized from the bone marrow, spleen, or primary tumor site (i.e., tumor-infiltrating neutrophils)? Answering this question will give us some clues about the instructive signals for neutrophil mobilization and recruitment, which can potentially be therapeutic targets for abrogating the recruitment of neutrophils to the omentum, preventing the formation of the premetastatic niche, and stopping the metastasis of ovarian cancer cells.

Emerging evidence indicates that neutrophils are not a homogenous population but consist of different subpopulations with distinct phenotypes and functions (Rosales, 2018). The diversification of neutrophils in tumor is well reported. However, there is still a lack of consensus regarding how to define the phenotypic and functional heterogeneity of neutrophils. Several recent studies, including our own, have provided a new framework for defining neutrophil subsets in the bone marrow (Kim et al., 2017; Evrard et al., 2018; Zhu et al., 2018). Conceivably, this framework can serve as a fundamental platform for the assessment of neutrophil subsets in various tissue compartments and the premetastatic niche during tumor progression. Such knowledge will help us understand how tumor induces neutrophil functional heterogeneity by determining whether the diversification of these cells arises from (1) the mobilization of neutrophils of distinct maturation stage from intra/extramedullary site, (2) bona fide neutrophil subsets induced by tumor-derived signals acting on early neutrophil precursors, or (3) the mature neutrophils activated by inflammatory signals.

Having shown that neutrophils play a key role in promoting premetastatic omental niche, Lee et al. (2018) further showed the underlying mechanism for this observation by demonstrating that neutrophil extracellular traps (NETs) released at the premetastatic omental niche are essential for governing the metastatic tropism of ovarian cancer cells. With these results, the authors proposed a model in which primary ovarian cancer cells trigger the early influx of neutrophil and the release of NETs in the premetastatic omental niche, and propose that these NETs will ensnare circulating ovarian cancer cells to this site. Of note, a seminal study from Albrengues et al. (2018) demonstrates that NETs are able to activate the proliferation of dormant cancer cells. With this notion, it will be interesting to investigate whether NETs will have other additional physiological and pathological effects on cancer cells, i.e., by promoting their survival and proliferation in the omental niche. Of interest, it is increasingly appreciated that neutrophils are not merely effector phagocytes but also play regulatory roles in various aspects of immune responses. Results from Lee et al. (2018) demonstrate the role of neutrophils in promoting ovarian cancer cell metastasis through NET formation, which undoubtedly may lead to more exciting clinical research toward modulating neutrophil function and NET formation/clearance for reducing the risk of cancer metastasis and recurrence in human patients.

To put the findings by Lee et al. (2018) in the context of the seed and soil theory, the authors have shown that neutrophil can serve as a "mobile fertilizer" that migrates to the premetastastic omental niche in response to primary ovarian cancer–derived signals, releasing NETs to make the niche "fertile" and permissive for the subsequent implantation of circulating cancer cells. In conclusion, this study has provided an invaluable insight into the sequence of cellular and molecular events leading to the metastasis of ovarian cancer, which reveals that blocking HEV-mediated neutrophil recruitment to the omentum and inhibition of NET formation may be of therapeutic value in improving ovarian cancer treatment.

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