# Differential mobilization of circulating neutrophil subpopulations in breast cancer metastasis

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Breast cancer is the most common cancer among Canadian women over the age of 20, representing 26% of all cancer cases in Canadian women. Metastatic breast cancer is the most advanced stage (stage IV) of the disease and it is largely incurable. Breast cancer cells display preferences for specific metastatic sites including the bone, lung, and liver. The liver represents a prominent site for breast cancer metastasis, with 50-70% of women with metastatic breast cancer developing hepatic metastases.

The steps involved in the metastatic cascade rely on reciprocal interactions between cancer cells and their microenvironment. Distinct immune infiltrates can either impair the metastatic process or conversely, assist in the seeding, colonization and growth of disseminated cancer cells. Within distal organs, immune cells and their mediators are known to facilitate metastasis formation. However, the contribution of tumor-induced systemic inflammation to metastasis and the mechanisms regulating systemic inflammation are not well characterized. Using lung and liver-metastatic variants of 4T1 breast cancer cells model, we have revealed that there are increased recruitment of myeloid-derived/granulocytic (Gr-1+) and neutrophils (NE+) in the lungs and livers of mice bearing lung and liver metastasis respectively. However, based on the Gr-1+ depletion studies, it was observed that infiltrating myeloid-derived/granulocytic cells, including neutrophils, were essential for the formation of liver metastases but not for lung metastases. Intriguingly, we have found that in peripheral blood, lung and liver metastases have the ability to mobilize differently the two distinct populations of high-density (HDNs) and low density neutrophils (LDNs) based on a density gradient centrifugation. In the peripheral blood of mice bearing liver metastases, there is a dramatic increase in the mobilization of LDNs compared to mice bearing lung metastases. Thus, we believe that liver metastatic breast cancer cells rely on interactions with neutrophils within the liver microenvironment for colonization and growth. Our results demonstrate the importance of investigating the role played by these two neutrophil subpopulations which may represent a new potential therapeutic strategy to inhibit metastatic diseases.