Shuttle service for metastatic cancer cells

While metastasis is responsible for the vast majority of cancer-related deaths, the biology underlying the metastatic process is poorly understood. Recent discoveries highlight the role of neutrophils as sparring partners of metastatic cancer cells, and their inhibition as a new potential strategy to reduce metastasis formation.

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The majority of cancer-related deaths are due to the spread of cancer cells throughout the body, a process called metastasis. While fundamental biological features that characterize this process are still under investigation, an important role is attributed to the "disobedience" of a patient's own immune cells. In a normal state, the immune system is protecting the human body against intruders, including those that are self-originating, such as cancer. However, upon disease development, occasionally, the very same guardian becomes a rogue, supporting circulating tumor cells (CTCs) that have detached from a cancerous lesion in their mission to establish metastasis elsewhere.

CTCs are essentially cancer cells that leave the primary tumor and enter the bloodstream, on their way to spreading the disease to distant sites. They are well-established metastatic precursors in many cancer types, and their presence has been strongly linked to a shorter survival of patients with cancer. CTCs can be found in the circulation as either individual cells, called single CTCs, or cellular groupings, referred to as CTC clusters, with the latter displaying a higher metastasis-forming ability. In some cases, these clustered CTCs are formed not only by tumor cells, but they are also containing other cell types such as white blood cells (WBCs).

In our study, we analyzed blood samples from 70 patients with metastatic breast cancer and five breast cancer mouse models, identifying single CTCs, CTC clusters and CTC-WBC clusters. We then assessed the gene expression pattern of isolated cells, individually, and found that the majority of WBCs within CTC-WBC clusters are neutrophils, i.e. immune cells typically involved in the protection against infectious agents. We also investigated the functional effects caused by the partnership between CTCs and neutrophils by comparing the characteristics of CTCs that were associated to neutrophils to those CTCs that were not. We found that neutrophil-associated CTCs were characterized by recurrent mutations and increased ability to proliferate. These features determine a high metastatic ability of CTC-neutrophil clusters, as we could demonstrate via direct metastasis-seeding assessment in preclinical models.

After discovering the advantage that CTCs gain from the alliance with neutrophils, our research focused on targeting possible vulnerabilities that characterize CTC-neutrophil clusters. To this end, we identified a number of messenger substances released by neutrophils to stimulate CTCs, including cytokines IL-1β and IL-6. Upon their elimination, we observed a clear abrogation of the pro-metastatic advantage conferred by neutrophils to cancer cells. Similarly, we identified VCAM1 as one of the major cell-cell junction components allowing CTCs and neutrophils to remain connected while circulating in blood. Once these holding units were genetically removed, the formation of CTC-neutrophil clusters was no longer possible.

In conclusion, we describe a new mechanism whereby cancer cells exploit a patient's own neutrophils to efficiently spread to distant sites. Described characteristics of CTC-neutrophil clusters provide new means of targeting them, suggesting new approaches aimed at reducing metastasis formation.

Original Article:

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