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Shuttle service for metastatic cancer cells

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ABSTRACT

Cancer cells are able to spread from the primary tumor to distant sites, in a process referred to as metastasis. Recent discoveries highlight the role of white blood cells as teammates of metastatic cancer cells, and their suppression 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 we still do not fully understand how metastasis works, 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, the very same guardian may become a rogue, for instance by supporting cancer progression from a primary tumor to a metastatic disease.

Circulating tumor cells, CTCs, are essentially cancer cells that leave the primary tumor and enter the bloodstream, on their way to spreading the disease to distant sites. 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. Interestingly, these CTC clusters can sometimes contain other, non-tumor cells such as white blood cells (WBCs). WBCs are the cells of the immune system that are normally designated to protect the body against invaders and diseases.

In our study, we analyzed blood samples from 70 patients with metastatic breast cancer as well as

mouse models, identifying single CTCs, CTC clusters and CTC-WBC clusters. We then assessed the characteristics 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 whether the partnership between CTCs and neutrophils had some effects on CTCs themselves. Surprisingly, we found that CTCs in partnership with neutrophils were able to better proliferate and metastasize.

Clearly, the next question was how could we target this partnership, and avoid CTCs from becoming so aggressive. To this end, we identified a number of messenger proteins released by neutrophils to stimulate CTCs. When we removed these substances with genetic tools or pharmacological agents, the pro-metastatic advantage that the neutrophils gave to CTCs was eliminated. Similarly, we identified holding units that, like Lego blocks, allowed CTCs and neutrophils to remain physically connected to each other while circulating in blood. We were able to remove these units genetically, and as a result, the formation of CTC-WBC clusters was no longer possible.

In conclusion, we describe a new mechanism whereby a patient's own neutrophils – meant to protect the human body – turn instead into helpers of the metastatic process by escorting CTCs during their journey. This newly discovered feature of neutrophils may provide new means of targeting them, leading to new approaches aimed at reducing metastasis formation.