A new hypothesis: some metastases are the result of inflammatory processes by adapted cells, especially adapted immune cells at sites of inflammation [version 1; peer review: 3 approved]

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Abstract
There is an old hypothesis that metastasis is the result of migration of tumor cells from the tumor to a distant site. In this article, we propose another mechanism for metastasis, for cancers that are initiated at the site of chronic inflammation. We suggest that cells at the site of chronic inflammation might become adapted to the inflammatory process, and these adaptations may lead to the initiation of an inflammatory tumor. For example, in an inflammatory tumor immune cells might be adapted to send signals of proliferation or angiogenesis, and epithelial cells might be adapted to proliferation (like inactivation of tumor suppressor genes). Therefore, we hypothesize that metastasis could be the result of an inflammatory process by adapted cells, especially adapted immune cells at the site of inflammation, as well as the migration of tumor cells with the help of activated platelets, which travel between sites of inflammation. If this hypothesis is correct, then any treatment causing necrotic cell death may not be a good solution. Because necrotic cells in the tumor micro-environment or anywhere in the body activate the immune system to initiate the inflammatory process, and the involvement of adapted immune cells in the inflammatory processes leads to the formation and progression of tumors. Adapted activated immune cells send more signals of proliferation and/or angiogenesis than normal cells. Moreover, if there were adapted epithelial cells, they would divide at a much higher rate in response to the proliferation signals than normal cells. Thus, not only would the tumor come back after the treatment, but it would also grow more aggressively.

Keywords
Metastasis, Cancer, Chronic inflammation, Adapted immune cells, Inflammatory processes, Immune system, Platelets, Wound healing process.
Many cancers arise from sites of chronic inflammation\(^1\). Immune cells inside the chronic inflammation site initiate tumor progression by releasing reactive oxygen or nitrogen species, which lead to DNA damage in epithelial cells\(^2\). Inflammation not only can cause mutation in epithelial cells\(^3\), but can also change their fitness\(^4\).

In chronic inflammation, T-cells might become adapted to send high levels of proliferation signals, and regulatory T-cells might have been changed to prevent their inhibition\(^5\). Effector T-cells also create an environment for tumor initiation and progression by releasing tumor-promoting cytokines IL-6\(^6\).

These findings suggest that cells at the site of chronic inflammation are adapted to the wound healing process. Immune cells are adapted to send signals of proliferation or angiogenesis, and tissue cells are adapted to proliferation (like inactivation of tumor suppressor genes). These adaptations lead to the initiation of a tumor.

If there are adapted immune cells, then we can look at metastasis from a new perspective. Any site of inflammation might recruit these adapted immune cells and serve as a new site for tumor initiation and progression by releasing tumor-promoting cytokines IL-6\(^6\).

There is evidence of metastasis to the site of injury. Two patients with squamous cell carcinoma of the lung developed distant localized metastatic disease at sites of physical injuries; one to the knee injured in an accidental fall six weeks earlier, and the other to portions of the liver injured in a mechanical fall two months earlier\(^7\). In a mice model of metastatic breast cancer, radiation-induced pulmonary injury lead to chronic inflammatory responses, and development of pre-metastatic niches\(^8\). In another mice model, hepatic ischemia-reperfusion injury increased the number of liver metastases of human pancreatic cancer (Capan-1) cells, which were injected into the mice spleen\(^9\). Several studies show that lung injury induced by the chemotherapy drug, bleomycin, increases lung metastases; they also observed tumor cell adherence to extracellular matrix and fibrin at injured areas\(^10\). Therefore we suggest that the sites of injuries are potential metastatic sites.

By querying published available data sets\(^11\), we calculate the probability of not detecting any CTCs in blood from patients with metastatic breast cancer, and the result is 0.6. That means there might be other phenomena, beside CTCs, that cause metastasis. Since, no CTCs were detected in the blood of 29% of metastatic breast cancer patients starting a first or new line of therapy, it is unlikely that treatments are responsible for not observing CTCs in blood\(^12\).

We hypothesize that chronic inflammation can cause adapted bone marrow derived cells (for example, adapted macrophages or T-cells) and/or adapted tissue cells (for instance, adapted epithelial cells or stromal fibroblasts) to lead tumor initiation and progression. If adapted immune cells are present, then the new site of inflammation might recruit these adapted immune cells and cause metastasis. Additionally, the new site of inflammation may recruit activated platelets. The activated platelets travel between sites of inflammation, including the site of inflammatory carcinoma. Tumor cells can link to adhesion receptors on platelets and travel to the new site of inflammation. The activated platelets start the wound healing process at the new site, which now includes some tumor cells. As the tumor cells respond to the wound healing signals more strongly than normal cells, new tumors would initiate in the site of inflammation (Figure 1).

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\(^{1}\) Tran et al.

\(^{2}\) Henson et al.

\(^{3}\) Chakraborty et al.

\(^{4}\) Mulligan et al.

\(^{5}\) Schuster et al.

\(^{6}\) Khattra et al.

\(^{7}\) Komatsuzaki et al.

\(^{8}\) Poirier et al.

\(^{9}\) Hino et al.

\(^{10}\) Sánchez-Madrid et al.

\(^{11}\) Mulligan et al.

\(^{12}\) Schuster et al.

\(^{13}\) Tran et al.

\(^{14}\) Mulligan et al.

\(^{15}\) Khattra et al.

\(^{16}\) Tran et al.

\(^{17}\) Mulligan et al.

\(^{18}\) Schuster et al.

\(^{19}\) Tran et al.

\(^{20}\) Mulligan et al.

\(^{21}\) Schuster et al.

\(^{22}\) Tran et al.

\(^{23}\) Mulligan et al.

\(^{24}\) Schuster et al.

\(^{25}\) Tran et al.

\(^{26}\) Mulligan et al.

\(^{27}\) Schuster et al.

\(^{28}\) Tran et al.
Competing interests
No competing interests were disclosed.

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There is more and more evidence that cancer metastases and inflammation share a common pathway. Therefore this hypothesis has a relevant scientific background. Prospective clinical trials looking at this issue will be welcome.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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The inflammatory nature of cancer, and especially metastases development, becomes a paradigm shift. This text summarizes well some new hypotheses and future challenges. Next steps to translate this in clinical trials are then needed.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of
expertise to confirm that it is of an acceptable scientific standard.

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This hypothesis has a potential to make a positive impact in cancer research and drug discovery. For cancer patients, it might help to accelerate both the development of promising therapies and the potential of personalized medicine — treatments based on an individual's unique immune deficiency. This is a very interesting and unique idea which needs more research.

Competing Interests: No competing interests were disclosed.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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