THE TREACHEROUS EFFECT OF THE LYMPH: HOW ITS FLUID CAN ADVANCE CANCER CELLS

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Brief message

Hi, my name is Mèlanie Reijnaers, master's student Biomedical Sciences and former scientific editor-in-chief of RAMS. During my bachelor's, I followed the cancer mechanisms and immunology course, which I found truly fascinating. Even though cancer is a devastating disease that has an impact on almost everyone's life, I believe the way metastasis occur is mesmerising. It reminds me of how quick species, and also our body, can evolve, which then again reminds me of all there is in the world. It makes me realise again that things might look straightforward but actually can be very complicated; it strengthens my curiosity. For this and more, I decided to write about the interesting phenomenon that is helping cancerous cells become more aggressive: the fatty lymphatic system. I hope you enjoy the read and that it makes you curious about how this phenomenon could be used for beneficial purposes.

Cancer, being the second leading cause of death worldwide, is a major public health problem [1]. Every day, thousands of researchers are trying to make a difference, to help patients fight the devastating effects the disease brings. This research is not only focussed on trying to create new treatments but also on figuring out the behaviour of the disease. Recently, in August 2020, Ubellacker *et al.* revealed the advantage that melanoma cells have when they migrate through the lymphatic system instead of the blood system [2]. This phenomenon is believed to have a pivotal role in the prognosis of cancer. For this reason, the intriguing mechanism behind this advantage will be discussed in this brief message, highlighting the importance of further research on this topic.

The migration of cancer cells from one tissue to another, leading to the formation of secondary tumours, is known as metastasis. Metastasis can occur through multiple routes of which the primary ways are transcoelomic spread (via the abdominal cavity), hematogenous spread (via the blood), lymphatic spread, and a combination of the latter two. Even though metastasis is common in cancer patients, the process is known to be inefficient as not many cells survive in the blood [3, 4]. The main reason for this inefficiency is the presence of oxidative stress in the blood [5]. As you might have already learnt during your studies, oxidative stress can induce cell death in multiple ways. Ubellacker *et al.* observed in *in vivo* assays that the melanoma cells are killed in the blood via a process called ferroptosis, which is induced by oxidative stress [2].

Ferroptosis is an iron-dependent form of cell death and causes lipid peroxidation. Polyunsaturated fatty acids (PUFAs) are in particular sensitive to the oxidative mechanism [6]. The rule goes as follows: the more unsaturated a phospholipid is, the more prone it is to undergo ferroptosis [7]. The oxidation of these PUFAs is the main reason why cells that transit through the lymphatic system have an advantage in spreading compared to cells that travel via the blood. To understand why this is the case, it is essential to know that the cell membrane usually contains many PUFAs. However, what is the reason for the advantage for cells that have been in the lymphatic system? Why does this milky-white, lymphocyte rich, fatty fluid lead to a beneficial effect for metastasis?

Well, that the lymphatic fluid is rich in triglycerides, alias fatty, is mostly the reason. Ubellacker *et al.* observed that malignant cells that entered the lymphatic system were significantly more enriched with oleic acid, which is a monounsaturated fatty acid (8.7 ± 0.9 (mean ± standard deviation)) [2]. This oleic acid, as well as other monounsaturated acids, acts as an inhibitor for ferroptosis by replacing and thereby reducing the density of PUFAs in the cell membrane. The reduced density of PUFAs leads to fewer available sites that can undergo ferroptosis. Therefore, when malignant cells enter the blood after they have been in the lymph nodes/vessels, the process of ferroptosis is avoided [2]. Subsequently, these cells have a higher chance to survive in the bloodstream leading to an increased risk of metastasis and a worse prognosis of the disease [Figure 1].

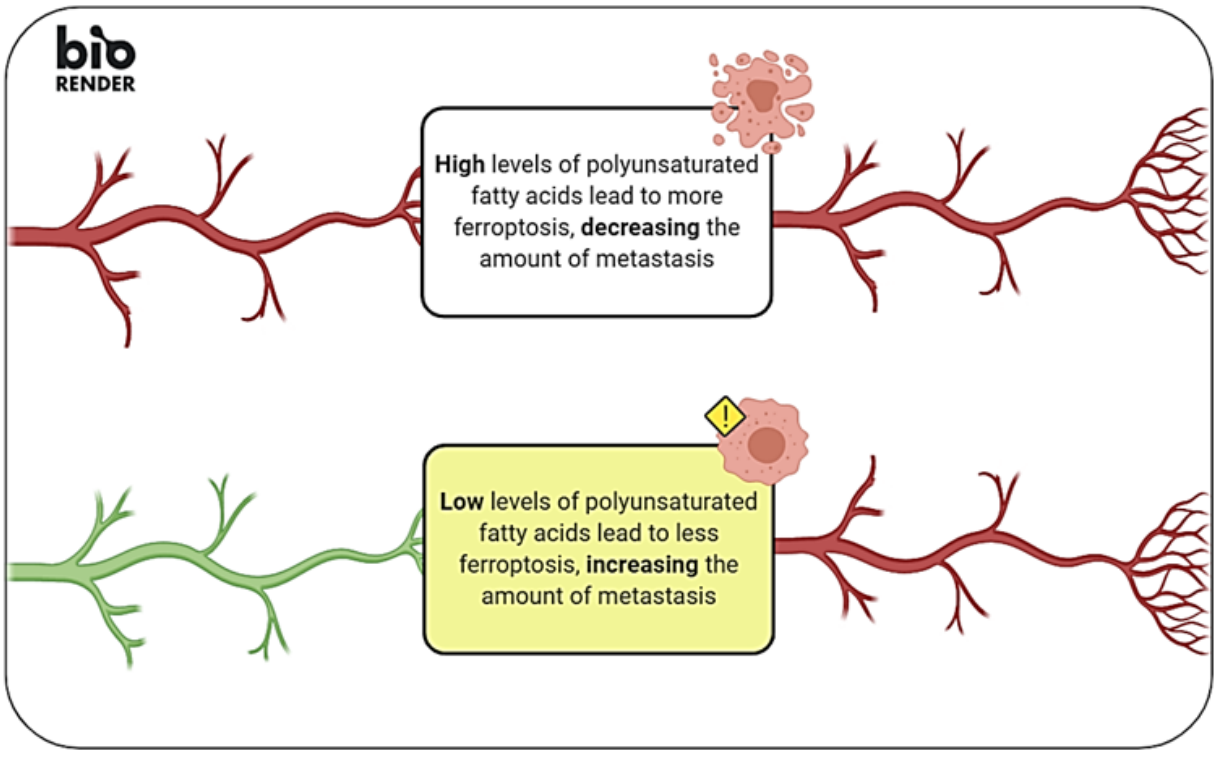

Figure 1: *How migration through the lymph can advance metastasis (created with biorender.com).*

This result was supported by additional results showing that melanoma cells in the presence of ferroptosis-inhibitor molecules led to the same amount of metastasis as the malignant cells that entered the lymphatic system without the inhibitor, suggesting that such cells did not undergo ferroptosis [2]. Moreover, the study of Ubellacker *et al.* measured a higher concentration of malignant cells in the lymphatic system compared to the blood system, which indicates as well that the fatty environment of the lymph contributes to an anti-cell-death mechanism [2]. These findings, and many more results from the study of Ubellacker and colleagues, provide a deeper understanding of the behaviour of malignant cells and lay the groundwork for future research into the protective environment of the lymph.

References

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EXAM QUESTION

Question 12

Do you want to test your knowledge? Try to answer the exam question below.

One of the biggest hurdles in cancer treatment is the occurrence of resistance to therapy in tumour cells. Which of the tumours mentioned below will respond to chemotherapy the fastest? Tumours with a...

A. large growth fraction
B. low growth fraction

The answer to this question can be found on page 34 in this journal.