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News & views

Tumour biology

Cancer cells stock up in lymph vessels to survive

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A cellular condition called oxidative stress can kill cancer cells. The finding that skin cancer cells evade such destruction using lipids acquired while passing through lymphatic vessels reveals a mechanism that boosts cancer spread.

The spread of cancer to distant parts of the body, such as to a compartment of the lymphatic system called a lymph node, indicates a poor prognosis for many types of the disease. However, for certain tumours, such as the skin cancer melanoma, lymph-node removal to prevent this spread does not increase survival time[1,2]. This finding might be explained by observations suggesting that the lymphatic system (which helps to maintain fluid balance and provides immune cells with a route for their movement) supplies vessels that offer an entry point through which spreading cancer cells can reach blood vessels[3,4] on their way to distant organs. Once they have travelled there, the cancer cells seed and form secondary tumours called metastases. Thus, lymph-node infiltration is not necessarily an endpoint, but rather a stopover on the cells' journey elsewhere. Yet the advantage of this detour has been unclear. Writing in *Nature*, Ubellacker *et al.*[5] reveal the boost that cancer cells receive in transit through the lymphatic system.

Cancer spread, or metastasis, is an inefficient process[6,7], and many cancer cells die in the bloodstream. A major contributory factor is oxidative stress in tumour cells. Studies have found that antioxidant treatment to block such stress causes an increase in the number of tumour cells in the bloodstream, and a rise in cancer spread to distant sites[8,9]. Oxidative stress can induce several types of cell death, but Ubellacker and colleagues show in mice that human or mouse melanoma cells in the bloodstream are killed by ferroptosis (Fig. 1), a cell-death mechanism that depends on lipid oxidation[10].

The authors report that pretreating melanoma cells with the ferroptosis-inhibitor molecule liproxstatin-1 resulted in more metastases when the cells were injected into the animals' bloodstream than when cells were not pretreated. By contrast, melanoma cells that disseminated through the lymphatic system produced the same degree of metastasis irrespective of liproxstatin-1 treatment, suggesting that such cells did not undergo ferroptosis. This finding indicates that, while in the lymphatic system, cancer cells acquire the ability to thwart a cell-death mechanism that usually impedes their progress if they move directly into the bloodstream. Moreover, Ubellacker *et al.* found that the number of melanoma cells in the animals' lymph fluid was higher than the number in the bloodstream, and that cells that disseminated through the lymphatic system were more likely to form metastases than were those that did not. This finding is remarkable, because it shows that only particular environments induce ferroptosis, and it suggests that melanoma cells that move through the lymph system and then exit into the bloodstream are more likely to survive than are cells that do not pass through the lymph.

Ferroptosis requires phospholipids in the cancer-cell membranes to be unsaturated (meaning that the molecules contain carbon–carbon double bonds that can be oxidized), and this type of cell death also requires iron[10]. The more unsaturated a phospholipid is (the more double bonds it has), the more prone it is to undergo oxidation. Thus, cell membranes that are enriched in saturated phospholipids (lacking double bonds) or monounsaturated ones (having only one double bond) are less likely to be sufficiently oxidized to induce ferroptosis than are membranes enriched in polyunsaturated lipids.

Many cells acquire polyunsaturated lipids and iron from their environment. Ubellacker and colleagues analysed blood

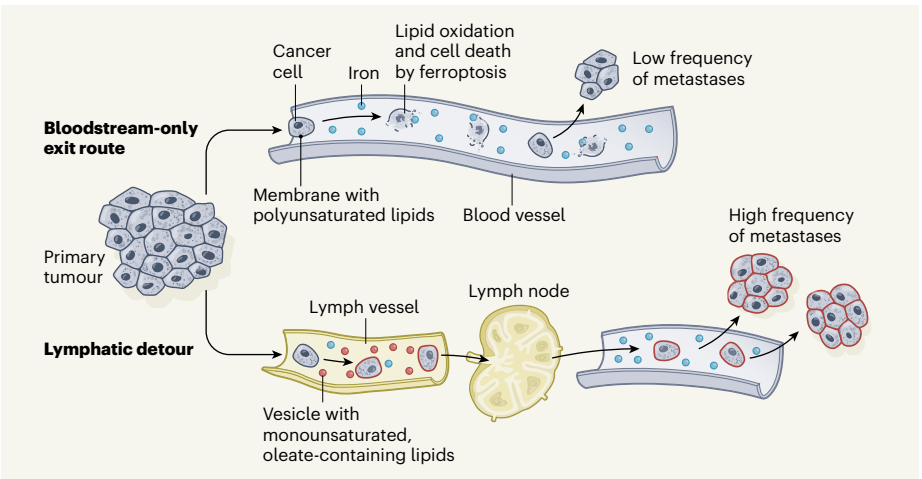

Figure 1 | A journey through lymph vessels boosts cancer cells. Ubellacker *et al.*[5] report studies in mice indicating that, if cancer cells exit a primary site of tumour growth through the bloodstream, the oxidative stress that they encounter makes them prone to undergo a type of cell death called ferroptosis. This process requires iron, which is present at high levels in the blood; the polyunsaturated lipids (those with more than one carbon–carbon double bond) in the membrane of cancer cells are oxidized during ferroptosis. The death of these cells limits the formation of distant metastases (tumours located far from the primary tumour). By contrast, Ubellacker and colleagues reveal that, if cancer cells exit the primary tumour through lymph vessels, they take up lipids containing oleate, a monounsaturated lipid (which contains only one carbon–carbon double bond), from the lymph fluid. When such cancer cells then enter the bloodstream from lymph nodes, this lipid helps the cells avoid ferroptosis, increasing the formation of metastases compared with the case for cancer cells that don't enter lymph vessels.

and lymph from their mice to discover how the lymph environment might protect melanoma cells from ferroptosis. They found that the main lipids in lymph were triglycerides, many of which contained oleate groups (which derive from oleic acid, a monounsaturated fatty acid), and that lipids containing oleate were generally more abundant in lymph than in the blood. The authors also observed that the animals' blood contained more than 100 times as much iron as did their lymph.

Ubellacker *et al.* took a dual approach to verifying the relevance of their findings. First, in mice in which human melanoma cells had been implanted under their skin, the authors isolated melanoma cells that had migrated from these subcutaneous tumours to the blood and to the lymph. They used mass spectrometry to analyse the molecules involved in tumour-cell metabolism (a metabolomics analysis). Consistent with the differences in the level of oleate-containing lipids between lymph and blood, the authors found that, of the 57 types of lipid detected in their experiments, the greatest difference between the melanoma cells from blood and lymph was in their levels of oleic acid. Moreover, melanoma cells pretreated with oleic acid survived better in the blood after intravenous injection into mice than did untreated melanoma cells.

Second, if iron was removed from the media surrounding melanoma cells grown *in vitro*, using the iron-chelator compound deferoxamine, this reduction in iron availability was enough to block ferroptosis. Together, these findings are consistent with the idea that the environment of the lymph, which is enriched in oleate-containing lipids, protects melanoma cells from ferroptosis, whereas the iron-enriched environment of the bloodstream contributes to its induction.

These results provide a first step towards understanding the protective environment of lymph, yet some questions arise. For example, to what extent do other saturated and monounsaturated fatty acids protect melanoma cells in lymph? What is the source of the oleate-containing triglycerides in lymph fluid? Is the lipid composition of the lymph altered, for example through clinical treatment or as a consequence of diet or in obesity?

Finally, the authors addressed the question of whether metastasis to the lymph nodes occurs before that to other locations because exposure to lymph induces a protective metabolic make-up that allows melanoma cells to spread. To investigate this, Ubellacker and colleagues isolated mouse melanoma cells from subcutaneous tumours and from tumours in lymph nodes, and injected these cells into the bloodstreams of mice. They found that melanoma cells from lymph nodes were more likely to form metastatic tumours than were cells from subcutaneous tumours. Moreover, cancer cells from the lymph nodes were less sensitive to treatment with the ferroptosis-inducing molecule erastin than were cells from subcutaneous tumours.

Further studies will be needed to confirm this intriguing possibility of a metabolic priming of cancer cells in lymph. For example, it would be useful to further validate this model by carrying out a metabolomics analysis comparing melanoma cells injected into the lymph node and then isolated from lymph and blood.

To what extent Ubellacker and colleagues' findings apply to tumour types other than melanoma, and to humans, remains to be determined. If the results are relevant to human disease, innovative ways must be found for them to have a therapeutic impact. For example, approaches might be developed to manipulate the ability of metastasizing cancer cells to incorporate and use these lipids for protection from ferroptosis, or to increase the sensitivity of tumour cells to ferroptosis, even in protective environments such as the lymphatic system.

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