Directed metastasis: breast to bone

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Introduction:

One of every three cases in women's cancer is in the breast, and 70% of these develops to bone metastasis. For this reason, in the last decade it has been proposed the possibility of directed metastasis, in which some primary tumours have a high probability to metastasize specific organs. In addition many authors talk about a specific gene expression signature in tumour cells which enables bone metastatic phenotype.[1]

The aim of this work is to make a bibliographic review about the most important factors to direct a breast tumour to bone metastase, from the role of many proteins to some environmental cells. And this way try to understand how the process develops.

1.Primary tumour:

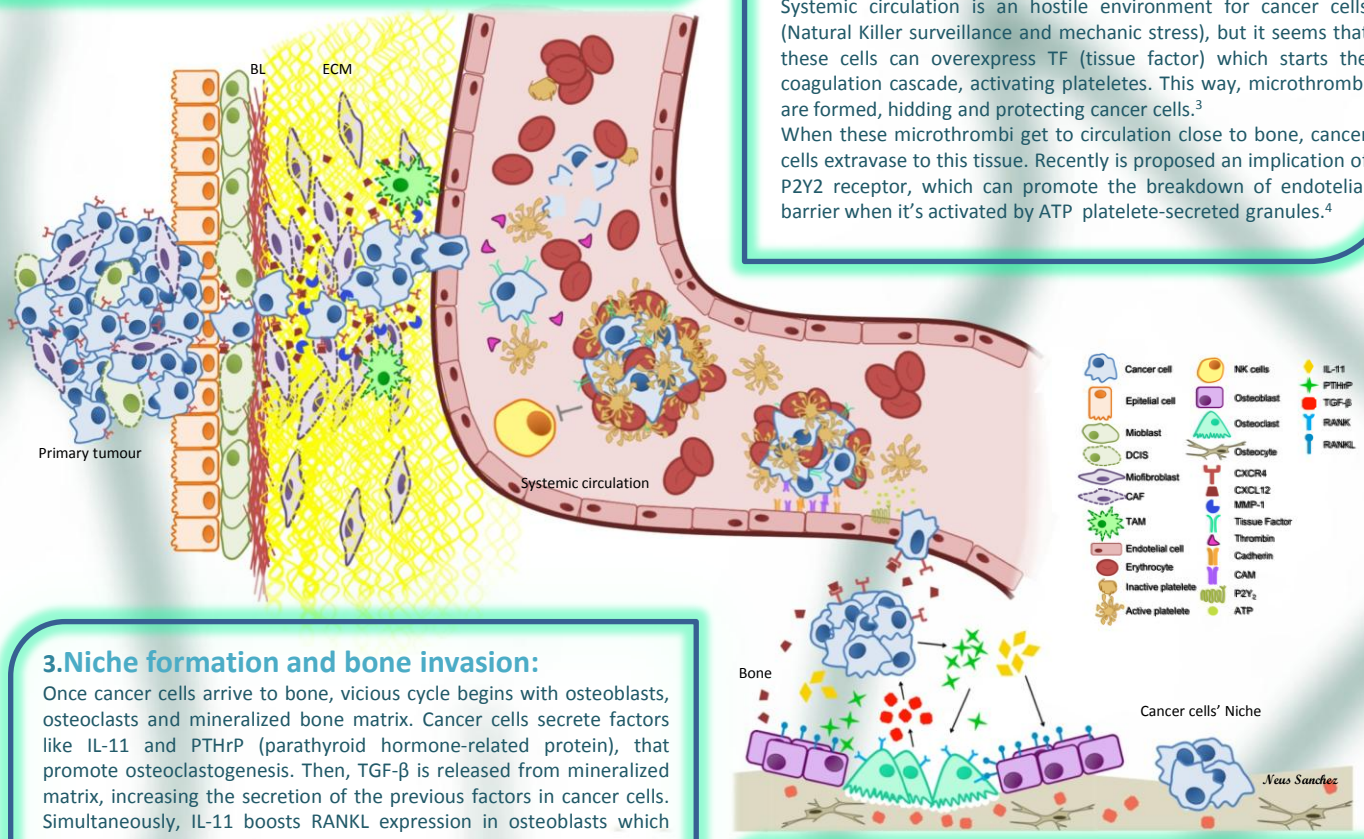
The primary tumour progression is due to tumour cell hallmarks and stroma cells which adopt a malignant phenotype to DCIS (ductal carcinoma in situ) cells, CAFs (carcinoma associated fibroblasts) and TAMs (tumour-associated macrophages). These cells secrete chemoattractants like CXCL12 and proteinases like MMP-1 (matrix metalloproteinase-1) which enable tumour cells to reach the circulation.[2]

2.Intravasation, circulation and extravasation:

Nowadays it's well known that cadherins have an essential role, allowing adhesiveness during intravasation and extravasation processes. Some types of cadherins are overexpressed in tumour cells and other are repressed. Also integrins and CAMs (cell adhesion molecule) are involved, but these processes are the less known.

Systemic circulation is an hostile environment for cancer cells (Natural Killer surveillance and mechanic stress), but it seems that these cells can overexpress TF (tissue factor) which starts the coagulation cascade, activating plateletes. This way, microthrombi are formed, hidding and protecting cancer cells.[3]

When these microthrombi get to circulation close to bone, cancer cells extravase to this tissue. Recently is proposed an implication of P2Y2 receptor, which can promote the breakdown of endotelial barrier when it's activated by ATP platelete-secreted granules.[4]



3.Niche formation and bone invasion:

Once cancer cells arrive to bone, vicious cycle begins with osteoblasts, osteoclasts and mineralized bone matrix. Cancer cells secrete factors like IL-11 and PTHrP (parathyroid hormone-related protein), that promote osteoclastogenesis. Then, TGF-β is released from mineralized matrix, increasing the secretion of the previous factors in cancer cells. Simultaneously, IL-11 boosts RANKL expression in osteoblasts which binds to osteoclast's RANK, increasing osteoclastogenesis.[5]

Finally, this high bone matrix resorption allow sites to create cancer cell niches.

Therapy:

- **Actual treatment:** surgery combinated with radio and chemotherapy. The main administered drugs are Biphosphonates and Denosumab.
- **Future approaches:** genic immunotherapy, based on helping the Imune System to recognise cancer cells.

Conclusions:

- It seems that breast tumour cells' tropism to metastasize in bone is mainly due to expression of many proteins with diverse functions (even more than the mentioned) which facilitate every step of the metastatic process.
- With this review I have accomplished the objective of describing some of the most important factors in each step of this directed metastasis, and to know the actual therapies.

Bibliography:

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