Tumor metastasis targets in bone

A novel strategy to inhibit breast cancer metastases to bone

Technology

Tumor metastasis remain the biggest therapeutically challenge in cancer research. Bone is one of the most prevalent sites of metastases in breast cancer patients. Patients with osteolytic metastases to the bone often experience lowered quality of live, pain, bone fractures and hypercalcemia. In the current paradigm of bone metastases bone degradation is the focal point, however we have shown that bone generation, through endochondral ossification, provides cancer cells with proliferative and migratory cues. We have analyzed molecules secreted from bone environment and identified CXLC5 to be responsible for cancer migration towards chondrocytes. We have further more developed short binding peptides (SBP) towards CXCL5 by phage display and shown that they can chondrocyte derived migration of cancer cells.

Innovation

- Bone anabolism is a potential mediator of breast cancer metastases to bone.
- Discovery that chondrocyte derived CXCL5 act as a chemoattractant on metastatic breast cancer cells.
- Identification of two SBP from phage display towards CXCL5.

Application

- Detection of cancer patients as risk for bone metastases
- Inhibition of bone specific metastases.

Developmental Status

- CXCL5 inhibition has been tested in vitro with antibodies and two 12 amino acid long peptides.
- The crystal structure of CXCL5 has been to map the binding site of the inhibitors to CXCL5

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Identification of tumor metastasis targets in bone

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Introduction

Bone is one of the most common sites for breast cancer metastasis and is causing severe health risks for patients. We found that the mature chondrocyte secretome provides a preferable environment for breast cancer metastasis formation, through secretion of chemotatic and mitogenic signals. Inhibition of CXCL5 through antibody and two novel CXCL5 binding peptides were able to reduce migration of metastatic breast cancer cells.

Experimental part

Primary human progenitor cells were differentiated into osteoblasts (Ob), osteoclasts (Oc) and chondrocytes (Ch).
MDA-MB-231 breast cancer cells were used as cellular model.
Small peptide CXCL5 inhibitors were identified through page display.
Structure of CXCL5 was identified through X-ray crystallization.

Results

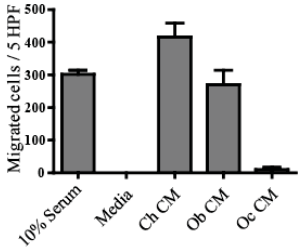

Figure 1: The Ch secretome induces migration of metastatic breast cancer cells.

Conditioned media (CM) from Obs, Chs and Oc were assays for migration induc-

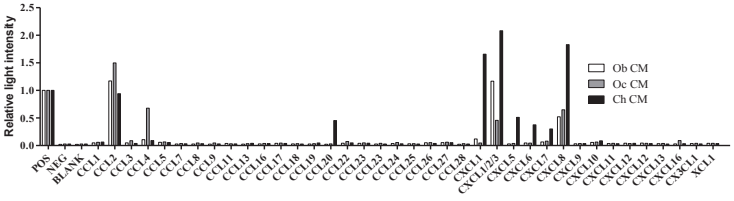

Figure 2: Identification chemokines secreted from the bone environment.

Chemokine secreted from Obs, Ocs and Chs has been identified via antibody arrays

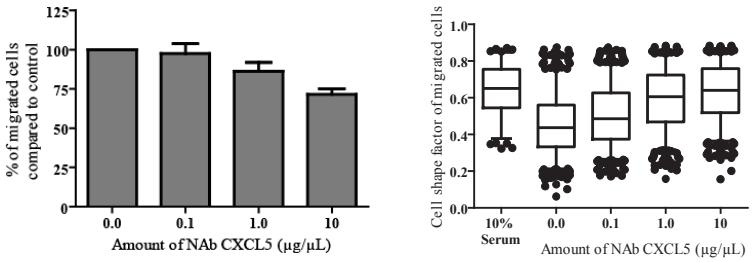

Figure 3: CXCL5 from the Ch secretome is responsible for cancer cell migration and changes in cell shape.

Using a neutralizing antibody (NAb) it has been shown that cancer cell migration could be reduced as well as changes in cell shape. The effect of the NAb was dose dependent.

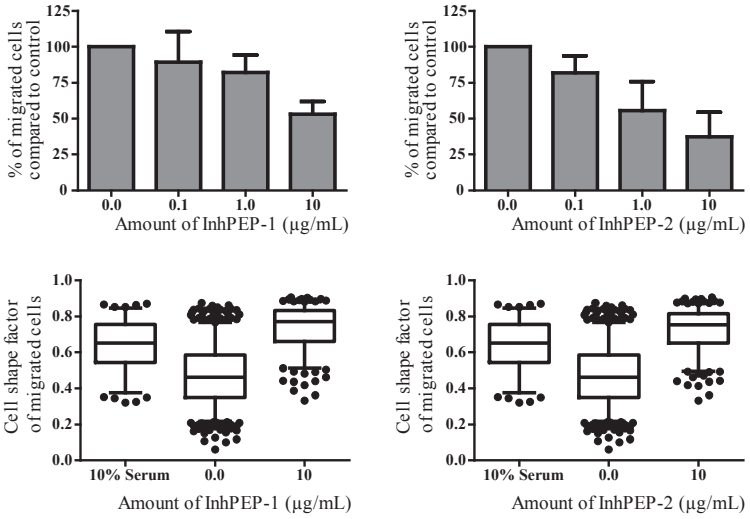

Figure 4: Novel small peptide inhibitors towards CXCL5 mirrors the effect of the CXCL5 NAb.

Two 12 amino acid sequences binding to CXCL5 has been discovered through phage display (InhPEP-1 and InhPEP-2). Both inhibitors mirrored the effect of the CXCL5 NAb.

Figure 5: Modelling of InhPEP-2 binding to CXCL5

The structure of CXCL5 has been elucidated via x-ray crystallization. The potential binding site of InhPEP-2 onto CXCL5 has also been identified via molecular modelling.

Conclusion

We have shown that Chs secrete pro-migratory molecules for breast cancer cell. We identified CXCL5 as being uniquely secreted by Chs in our system. Inhibition of CXCL5, with a NAb, resulted in a decreased cancer cell migration, this could be titrated with increasing amounts of NAb. Two 12 amino acid long peptides binding to CXCL5 were discovered through phage display. The two peptides mirrored the effect of the CXCL5 NAb, and the effect was likewise concentration dependent.
A potential interaction site between CXCL5 and InhPEP-2 was found through molecular modelling.

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We would like to thank Prof. Ivan Martin (Uni Basel) for providing us with protocols for differentiation of primary cells.
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