PRESS RELEASE

Disseminated breast cancer cells use bone marrow growth factors for metastasis formation

Researchers of the University Hospital Regensburg and of Fraunhofer ITEM have published new findings on the mechanism of metastatic spread in "Nature Communications.

Why does it often take years or even decades before metastases become manifest in breast cancer patients, although cancer cells disseminate into other organs such as bone marrow as early as shortly after formation of the primary tumor? A team of researchers headed by Professor Christoph Klein at the University of Regensburg and at Fraunhofer ITEM in Regensburg addressed this question. The researchers have demonstrated that disseminated cancer cells can acquire stem cell-like properties by interpreting signals from the bone marrow environment, enabling them to form metastases. "These findings may reveal an Achilles' heel of disseminated cancer cells and could enable completely new therapeutic approaches, such as inhibition of such signals from the microenvironment colonized by disseminated cancer cells", says Professor Klein, Senior Professor of Experimental Medicine and Therapy Research at the University of Regensburg and Division Director of Personalized Tumor Therapy at Fraunhofer ITEM.

Cancer is a fatal disease, with worldwide steadily increasing incidences due to the increasing age of the Western population. The leading cause of death in patients diagnosed with cancer is metastasis formation in vital organs, for example in bone marrow, lung, brain and liver. Even though dissemination of cancer cells in breast cancer patients occurs already early during primary tumor formation, not all patients with disseminated cancer cells develop metastatic disease and it can take years or even decades for metastases to become manifest. The early stage of dissemination on the one hand and the prolonged clinical latency periods prior to metastasis on the other hand raise the question as to what factors either promote or inhibit metastasis formation from disseminated cancer cells.

To address this question, Klein and his team screened diagnostic bone marrow biopsies from 246 patients with early-stage breast cancer for disseminated cancer cells, isolated these cells and performed molecular analyses using the latest single-cell technologies. These investigations posed special technical challenges, given that disseminated cancer cells are particularly rare. They are detected in the bone marrow of only 20 to 30 percent of breast cancer patients at an early stage of the disease, that is when metastases have not yet become evident, and their frequency is only about one cancer cell per one to ten million bone marrow cells. This situation required not only dedicated clinical partners at the Caritas Hospital St. Josef in Regensburg and at Ludwig Maximilians University in Munich, but also the use of highly specialized technologies. These includ-

Editor
Cathrin Nastevska | Fraunhofer Institute for Toxicology und Experimental Medicine, ITEM | Phone +49 511 5350-225 |
Nikolai-Fuchs-Straße 1 | 30625 Hanover | www.item.fraunhofer.de | cathrin.nastevska@item.fraunhofer.de |

ed sensitive methods for detection of disseminated cancer cells in diagnostic bone marrow biopsies, available at the Chair of Experimental Medicine and Therapy Research of the University of Regensburg, and cutting-edge sequencing technologies allowing molecular biological information to be obtained from minute cell quantities or even single cells – a core competence of the Regensburg-based Fraunhofer ITEM Division of Personalized Tumor Therapy.

The researchers were able to show that the disseminated cancer cells detected in bone marrow responded to the growth factor interleukin-6, which is available in large quantities in the normal bone marrow environment. In cell culture models using mammary epithelial cells, they demonstrated that the interleukin-6 signal endows these cells with stem cell properties, which are believed to be essential for metastasis formation. In addition, the researchers provided evidence that certain niches in bone marrow render disseminated cancer cells unresponsive to interleukin-6 signaling. This may explain why some patients do not develop metastases at all or only after a very long time, although thousands of cells from the primary tumor already disseminated into the bone marrow prior to tumor resection. Comparison of cancer cells from the bone marrow of non-metastatic patients with cancer cells from blood samples of metastatic patients suggests that cancer cells can acquire genetic alterations, for example in the phosphatidylinositol-3-kinase, during their further development in the bone marrow and thereby become independent of environmental signals from the bone marrow and thus increasingly malignant.

These findings have important implications for the development of new adjuvant therapies. Adjuvant therapies try to eliminate disseminated cancer cells already at an early stage of the disease, i.e. after removal of the primary tumor, and thereby to prevent the onset of lethal metastases. It stands to reason that cancer cells might differ in their sensitivity to certain drugs during the different phases of cancer development, which complicates anti-cancer treatments. In early-stage cancer, an Achilles' heel of disseminated cancer cells could be their dependence on microenvironmental signals promoting their survival and outgrowth. It may well be that at this early stage of disease, disseminated cancer cells are more sensitive to already available drugs, if they are additionally deprived of microenvironmental growth factors or activation of their growth by bone marrow-derived factors is inhibited. Professor Klein’s team hopes that the development of metastases in breast cancer patients can thus be prevented in the future.

Original publication:

Werner-Klein M, Grujovic A, Irlbeck C, Obradovic M, Hoffmann M, Körkel-Qu H, Lu X, Treitschke S, Köstler C, Botteron C, Weidele K, Werno C, Polzer B, Kirsch S, Gužvić M, Warfsmann J, Honarnejad K, Czyz Z, Feliciello G, Blochberger I, Grunewald S, Schneider E, Haunschild G, Patwary N, Guetter S, Huber S, Harbeck N, Rack B, Buchholz S, Rümmele P, Heine N, Rose-John S and Klein CA, Interleukin-6 trans-signaling is a candidate mechanism to drive progression of human DCCs during clinical latency. In: Nature Communications 2020, DOI: https://doi.org/10.1038/s41467-020-18701-4

Technical contact:
Fraunhofer ITEM
Division Director of Personalized Tumor Therapy
Prof. Dr. Christoph Klein
christoph.klein@ukr.de

Press contact:
Fraunhofer ITEM
Dr. Cathrin Nastevska
Phone 0511 5350-225
cathrin.nastevska@item.fraunhofer.de

Vita Prof. Dr. Christoph Klein

Christoph Klein obtained his medical degree from the Ludwig Maximilians University (LMU) in Munich (Germany) in 1998 and established an independent research group in 2001. After habilitation, he was promoted to Professor of Oncogenomics at the University of Regensburg in 2006. Since 2010, he has been holding the chair of Experimental Medicine and Therapy Research there and was appointed Division Director of Personalized Tumor Therapy at Fraunhofer ITEM in 2011.
Klein has received several awards, including:

- BioFuture Award (2001)
- Dr. Josef Steiner Award (2011)
- German Cancer Award (2014)
- Gerhard-Domagk Award (2017)
- I. J. "Josh" Fidler Innovation in Metastasis Research Award from the Metastasis Research Society (2018)

Isolation of single cancer cells previously obtained from patient material by microscopy. The monitor shows the glass capillary with the cell that will then be subject to molecular biological analysis.