Press Release

How cancer cells escape crowded tumors

(Vienna, 16.10.2020) **When trapped in a crowded environment, cells of the human body try to escape. Scientists now discovered that it is the cell nucleus, which triggers the "evasion reflex". This reflex is activated once cell compression exceeds the size of the nucleus. Published in the highly renowned journal *Science,* this unexpected finding could help to predict treatment response and metastatic spreading of tumors.**

Like people, cells in the human body protect their personal space. They seem to know how much space they need, and if it gets too tight, most cells prefer to break free. The mechanism enabling cells to evade crowded environments appears to involve an unusual player – the cell nucleus. This is what researchers from St. Anna Children's Cancer Research Institute Vienna, King's College London, Institute Curie Paris, and ETH Zürich in Basel showed in their recent work (https://science.sciencemag.org/content/370/6514/eaba2894).

Tissue cells protect their "personal space"
The human body consists of trillions of cells growing in confined volumes, which often leads to cell crowding. The crowding effect is exacerbated when cell growth and proliferation are out of control during tumor formation. This creates a compressive microenvironment for the constituent cells. How do tumor cells cope with the lack of space and compressive stresses? Answering this question, the investigators found that the cells are able to sense environmental compression.
To do so, they utilize their largest and stiffest internal compartment, the nucleus. Squeezing cells to the degree that physically deforms the nucleus causes the nuclear membranes to unfold and stretch. These changes are detected by specialized proteins, activating cellular contractility. The ability to develop contractile forces helps squeezing the cell out of its compressive microenvironment in an "evasion reflex" mechanism. Therefore, the study proposes that the nucleus operates as a ruler (see the accompanying illustration). It allows living cells to measure their personal space and trigger specific responses once the space becomes violated.

Fat restrictions to target metabolic vulnerability in cancer?
As the scientists describe in the paper, Ca^{2+}-dependent phospholipase cPLA2 is a protein, which senses nuclear membrane stretch upon cell compression. The lead author Alexis Lomakin, PhD, emphasizes that cPLA2 represents a druggable target. "Pharmaceutical companies are currently testing small molecule inhibitors of cPLA2. Based on our data, downregulating the activity of cPLA2 in tumor cells might interfere with their ability to escape the primary tumor and metastasize to distant locations", explains Dr. Lomakin.
cPLA2-inhibitors prevent the production of arachidonic acid (ARA), which subsequently affects cell migration, growth, and survival. However, ARA can also be obtained by cells from their environment. The Western diet, for instance, is a potent source of omega-6 fatty acids, such as ARA. Dietary fat restriction and consumption of omega-3 instead of omega-6 fatty acids could synergize with cPLA2 inhibitors to effectively attenuate tumor cell escape from overcrowded areas. "Testing these hypotheses is an exciting direction for future research", concludes Dr. Lomakin.

Potential predictive marker for chemo-resistance
Identifying the cell nucleus as an active player that rapidly converts mechanical inputs into signaling or metabolic outputs is surprising. Until today, the nucleus was considered as a passive storehouse for genetic material. "We are

very excited about what comes next", says Dr. Lomakin. According to him, high degrees of nuclear deformation could be predictive of metastatic potential and resistance to chemotherapy and immunotherapy.
"For many years, pathologists have been evaluating changes in the shape of the nucleus to discriminate between different stages of tumor growth; however, how these structural-mechanical alterations of the nucleus functionally impact cancer cells remained completely unexplored", says Dr. Lomakin.

Picture: Alexis Lomakin, PhD
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Figure: Cell nucleus deformation triggers a signaling cascade for cancer cell escape
Copyright: Wojciech Garncarz (St. Anna Children's Cancer Research Institute)

Publication
The nucleus acts as a ruler tailoring cell responses to spatial constraints
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About Alexis Lomakin, PhD
Alexis Lomakin, PhD, is a Program Leader & Deputy Lab Head in the academic group of Prof. Kaan Boztug, MD, at St. Anna Children's Cancer Research Institute/CCRI in partnership with Ludwig Boltzmann Institute for Rare & Undiagnosed Diseases/LBI-RUD, the CeMM Research Institute for Molecular Medicine of the Austrian Academy of Sciences, and Medical University of Vienna (Vienna, Austria). Prior to taking up the position in Vienna, Dr. Lomakin was a Junior Group Leader at King's College London (London, UK) and a Staff Scientist at the Institut Curie (Paris, France). He obtained his PhD in Cellular and Molecular Biology from Lomonosov Moscow State University (Moscow, Russia), and the University of Connecticut (Farmington, CT, USA). Dr. Lomakin pursued his postdoctoral training in Quantitative Cell Biology at Harvard University (Boston, MA, USA).

The scientist received prestigious fellowships and awards including the London Law Trust/LLT Medal and Fellowship for scientific excellence, innovation & vision (UK), the Marie Skłodowska-Curie and PRESTIGE Fellowships (EU/France), and the Leukemia & Lymphoma Society/LLS Postdoctoral Fellowship (USA).

About St. Anna Children's Cancer Research Institute, CCRI
The CCRI is an internationally renowned multidisciplinary research institution with the aim to develop and optimize diagnostic, prognostic, and therapeutic strategies for the treatment of children and adolescents with cancer. To achieve this goal, it combines basic research with translational and clinical research and focus on the specific characteristics of childhood tumor diseases in order to provide young patients with the best possible and most innovative therapies. Dedicated research groups in the fields of tumor genomics and epigenomics, immunology, molecular biology, cell biology, bioinformatics and clinical research are working together to harmonize scientific findings with the clinical needs of physicians to ultimately improve the wellbeing of our patients.
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About Ludwig Boltzmann Institute for Rare and Undiagnosed Diseases (LBI-RUD)
LBI-RUD was founded in 2016 in a joint effort of Ludwig Boltzmann Society, CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences, Medical University of Vienna, and St. Anna Children's Cancer Research Institute. The three founding partner institutions, and CeRUD Vienna Center for Rare and Undiagnosed Diseases, constitute LBI-RUD's most important collaboration partners.
Research at LBI-RUD focuses on the deciphering of rare immunological, hematopoietic, nervous, dermal, gastro-intestinal, and hepatic diseases. Those studies provide unique insights into human biology, and are the basis for the development of tailored therapeutic concepts in the sense of the personalized medicine of the future.
The mission of LBI-RUD is – together with its partner institutions – to sustainably develop and maintain research infrastructure integrating scientific, societal, ethical, and economical aspects of rare diseases.
www.rare-diseases.at

About CeMM Research Center for Molecular Medicine of the Austrian Academy of Sciences
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https://cemm.at/

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