Colorectal cancer initiation and progression: the role of low oxygen

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Scientists from the University of Luxembourg together with researchers from the Integrated Biobank of Luxembourg (IBBL) and the Luxembourg Institute of Health (LIH) have recently demonstrated the mechanisms by which low oxygen levels trigger series of cellular changes leading to the survival, renewal and growth of colorectal cancer cells. The findings further reinforce current knowledge on the initiation and progression of the disease and may contribute to opening up new treatment avenues for patients.

Low oxygen levels in cancer cell survival

Colorectal cancer (CRC) is one of the most common types of cancers globally, being responsible for about 600,000 deaths annually. Advances in the understanding of its initiation and development have been provided by the identification of a specific subtype of cancer cells displaying tumour-initiating properties. These so-called tumour-initiating cells (TICs) or cancer stem cells (CSCs), which are also associated with cancer progression and increased resistance to anti-cancer drugs, are often found in low oxygen regions within the tumour, named hypoxia. Indeed, this situation of hypoxia—a condition of inadequate oxygen availability at the tissue level, resulting from an imbalance between oxygen supply and consumption by diving cells—has been shown to be associated with an aggressive cancer behavior, resistance to chemo- and radiotherapy, as well as an increased rate of tumor recurrence, consequently resulting in poor patient outcomes.

In this context, researchers from the Life Sciences Research Unit (LSRU) of the University of Luxembourg—together with the Tumor Immunotherapy and Microenvironment group of the Luxembourg Institute of Health (LIH), the Integrated Biobank of Luxembourg (IBBL), the Centre Hospitalier Emile Mayrisch (CHEM), the Laboratoire National de Santé (LNS) and the Luxembourg Centre for Systems Biomedicine (LCSB)—used TICs enriched patient-derived CRC cultures to elucidate the link between hypoxia, TICs and increased cancer malignancy. Namely, the team observed that hypoxia triggers the expression of a series of genes involved in the activation of autophagy in TICs. Autophagy is a cellular survival process triggered by stress conditions, such as starvation and low oxygen levels, that causes the 'autodigestion' of intracellular proteins and other components, which become an energy source to sustain cellular metabolism. The team also found that hypoxia-induced autophagy in turn induces specific modifications to a particular protein, ezrin (EZR), through the action of an intermediate protein (PRKCA). This modification 'activates' the EZR protein, which is known to be involved in cell survival, and therefore results in the increased resistance and self-renewal capacity of TICs, leading to metastatic tumour growth.

As part of the study, IBBL was involved in the set-up of the collection of colon tissue samples and in the immunohistochemical staining—from the optimisation of the antibodies to the staining and analysis of tissue slides. Researcher from LIH performed microarray gene expression profiling experiments, while the Tumor Immunotherapy and Microenvironment (TIME) unit of the Department of Oncology, headed by Dr. Bassam Janji, was involved with the LSRU to understand the extent of autophagy in TICs under hypoxia.

"We are honored to have contributed to this study. It represents a true example of multidisciplinary collaboration between all major players in the national biomedical research landscape and of high-impact research

'made in Luxembourg'," says Dr. Yervand Karapetyan, Pathologist at IBBL.

"Up until now, we knew that hypoxia and autophagy are associated with an increased tumour malignancy, but the mechanisms and the exact relationship between these factors were still unclear. Our work provides an explanation to this research conundrum. We showed that TICs upregulate autophagy under low oxygen conditions to survive this stress, which in turn 'switches on' the EZR protein involved in their survival and growth," explains Dr. Elisabeth Letellier, Principal Investigator in the Life Sciences Research Unit of the University of Luxembourg and corresponding author of the publication. "The study also suggests that this link between hypoxia, autophagy and EZR activation could be 'broken," either by genetically targeting the genes involved in triggering autophagy, or by pharmacologically inhibiting the PRKCA and EZR proteins. This would reduce the tumour-initiating action of TICs, slowing down its progression and thus potentially representing a promising therapeutic strategy for cancer patients," she concludes.

More information: Komal Qureshi-Baig et al. Hypoxia-induced autophagy drives colorectal cancer initiation and progression by activating the PRKC/PKC-EZR (ezrin) pathway, *Autophagy* (2019). DOI: 10.1080/15548627.2019.1687213

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