

Normalizing tumor oxygen supply could be key factor in the fight against cancer

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Killer T cells surround a cancer cell. Credit: NIH

The lack of oxygen in tumor cells changes the cells' gene expression, thereby contributing to the growth of cancer. This is the main conclusion of a research project led by professor Diether Lambrechts and Dr.

Bernard Thienpont (VIB-KU Leuven), which was published in the renowned scientific journal *Nature*. The findings are far-reaching, as the study also proved that maintaining a proper oxygen supply in tumors inhibits these so-called 'epigenetic aberrations'. The paper's insights could eventually lead to new anti-cancer drugs that target blood vessels or the epigenetic aberrations.

Cancer onset is generally well-understood: due to chance or carcinogenic factors, a single cell's DNA mutates, followed by the rapid expansion of the abnormal cell. These genetic mutations disturb normal cell function, but are beneficial for the growth and survival of cancer cells. But apart from these genetic changes, tumors cells also differ epigenetically, which has to do with how genes are expressed rather than the genes themselves.

Pertinent to a wide range of cancers

Although epigenetic changes don't affect the genetic code, they can strongly disturb gene function in a similar way, to the benefit of cancer cells. But until now, the origins of these [epigenetic changes](#) mostly remained a mystery. Scientists from the lab of professor Lambrechts investigated one frequent epigenetic alteration: hypermethylation, or the excessive addition of [methyl groups](#) to DNA. Hypermethylation silences the expression of [tumor](#) suppressing genes, thereby enabling the aberrant behavior of cells and the excessive growth of tumors.

Diether Lambrechts (VIB-KU Leuven): "Our study shows that these [epigenetic alterations](#) are caused by the environment of the tumor, and more specifically by oxygen shortage - which we call 'hypoxia'. Oxygen is required by the enzymes that normally remove the methyl groups from the DNA. When there is oxygen shortage, too much methylation is retained, causing hypermethylation. Even more, hypoxia explains up to half of the hypermethylation in tumors. While we dedicated much of our

efforts to breast tumors, we also demonstrated that this mechanism has a similarly broad impact in bladder, colorectal, head and neck, kidney, lung and uterine tumors."

Diagnostic and therapeutic uses

Uncovering the link between oxygen shortage and tumor growth was the result of the analysis of over 3,000 patient tumors. As a next step, the researchers verified another assumption: would interfering with tumor oxygen supply strike a blow against the progression of cancer? They were pleased to see this hypothesis confirmed: using mice, they proved that normalizing the blood supply is sufficient to stop the epigenetic alterations from occurring.

Bernard Thienpont (VIB-KU Leuven): "Our new insights can have a potentially huge impact on cancer management. First of all, we could use epigenetic aberrations to monitor the [oxygen supply](#) to a tumor, allowing us to better predict tumor behavior and make more informed treatment decisions. Secondly, it sheds new light on existing blood vessel targeting therapies. They don't only help deliver chemotherapy to the tumor, but also inhibit new epigenetic aberrations. This could in turn help make relapses less aggressive, and thus prove to be therapeutically beneficial."

Next steps

The first ambition is already in full swing: the VIB lab is now testing whether analyzing tumor DNA can be used to predict tumor oxygenation. The scientists are also engaged in new research that focuses on blood vessel normalizing therapies. "We want to know whether it's not just possible to inhibit, but maybe even to reverse some of these epigenetic aberrations. Following through on these and other new research avenues gives us great faith in the future of cancer research,"

concludes prof. Lambrechts.

More information: Tumour hypoxia causes DNA hypermethylation by reducing TET activity. *Nature*, 2016.

Provided by VIB (the Flanders Institute for Biotechnology)

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