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Anti-tumor activity of immune cells can be restored

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The Leuven-based VIB researchers have revealed a mechanism that explains why the anti-tumor activity of specific immune cells called macrophages is suppressed during tumor growth. They have also demonstrated that blocking the protein Nrp1 can restore this anti-tumor immune response. This is a first. Nrp1 may provide an important hub for the development of new therapies against cancer.

Max Mazzone: "For many years the biological processes which lead to the coordinated navigation of blood vessels and nerves have been studied. The first observations come, in fact, from the Belgian anatomist Andreas Vesalius. So we were surprised to discover that immune cells follow the same

signals of blood vessels and nerves to position themselves within the tumor cell and, in doing so, contribute to tumor growth. By blocking these signals, we can once again turn the immune cells against the tumor."

Macrophages and cancer

Macrophages are important cells within the immune system. Among other things, they are responsible for cleaning up pathogens, such as bacteria and viruses. Macrophages, however, also appear to play an important and complex role in the occurrence and metastatization of cancer.

Macrophages that migrate to the tumor are called tumor-associated macrophages or TAMs for short. Extensive infiltration of TAMs into the tumor is often correlated with a poor prognosis in various cancers. These TAMs suppress the immune system and stimulate blood vessel formation thereby stimulating the growth of the tumor. On the other hand, there are also studies that show just the opposite effect, reaching the conclusion that TAMs have an anti-tumor effect.

The opposing functions of TAMs in the development of tumors arise the question whether there are specific factors within the micro-environment of the tumor which dictate the phenotype of these TAMs.

Neuropilin-1 (Nrp1)

Andrea Casazza and his colleagues, under the direction of Massimiliano Mazzone, studied the mechanism that is responsible for the opposing phenotypes of TAMs. Their study showed that the protein neuropilin-1 (Nrp1) is crucial for the localization of TAMs inside hypoxic tumor regions, which strengthens the pro-tumoral characteristics of TAMs.

Consequently, they discovered that by blocking Nrp1, macrophages were no longer able to migrate inside hypoxic regions in the tumor. It is in this way that the anti-tumoral activity of the macrophages is restored. Less suppression of the immune response and less blood vessel formation in the tumor leads to less tumor growth.

Impact of this research

This pre-clinical study from Professor Mazzone and his colleagues reveals a new molecular axis that may offer interesting therapeutic opportunities for the treatment of pancreatic cancer, breast cancer and lung cancer, among others. The goal of a therapy like this is to restore

the anti-tumor phenotype of

macrophages. After all, macrophages are cells that are normally part of our immune systems.

Furthermore, these results also have an important prognostic value—the positioning of macrophages in hypoxic tumor regions would be an indication of a poor prognosis, while the localization of macrophages in normoxic regions of the tumor could predict a better disease outcome.

More information: This research appears in the journal *Cancer Cell*: Casazza et al., Impeding macrophage entry into hypoxic tumor areas by Sema3A/Nrp1 signaling blockade inhibits angiogenesis and restores anti-tumor immunity).

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