A double block of blood vessels to starve cancerous tumors

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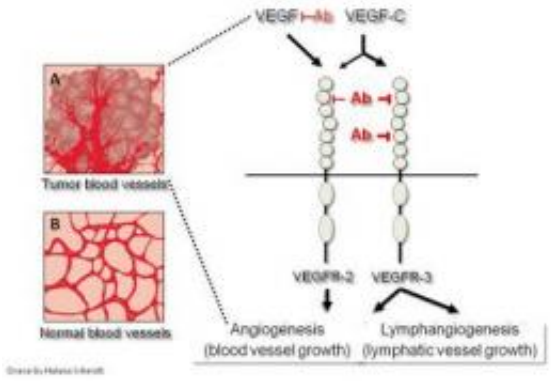

A shows an illustrated view of blood vessels in a cancerous tumor, B shows blood vessels in healthy tissue. On the right, signals for blood vessel growth are shown schematically. The main inducers of blood vessel growth are vascular endothelial growth factor (VEGF) and VEGF-C. The signals are mediated via VEGF receptor-2 and VEGFR-3, as illustrated with the arrows. The sites of action of the inhibitory antibodies (Ab) are indicated in red. The antibodies against VEGF are already used in the treatment of patients. Antibodies against VEGFR-2 are in clinical trials. The newly discovered antibody combination providing increased efficacy is directed against VEGFR-3. Credit: Drawn by Helena Schmidt

A novel strategy of blocking the growth of blood vessels with antibodies should result in improved treatment of cancerous tumors.

The growth of new blood vessels from pre-existing vasculature is called angiogenesis. In adults, angiogenesis occurs only during wound healing

and menstrual cycling, but is abundant and harmful in cancerous tumors and the old-age eye disease frequently leading to blindness called age-related macular degeneration (AMD). Without the formation of new blood vessels, tumors cannot grow beyond a small size due to lack of oxygen and nutrients. Inhibition of angiogenesis is used in the treatment of cancer and AMD, but not all cancer patients respond, while others become refractory to therapy.

Academy professor Kari Alitalo and co-workers at the University of Helsinki, Finland, have previously shown that antibodies directed towards vascular endothelial growth factor receptor (VEGFR)-3, found on the surface of endothelial cells lining vessels, can inhibit lymphatic metastasis by 50-70% in preclinical tumor models. Furthermore, antibodies that inhibited the growth factor VEGF-C from binding to the VEGFR-3 suppressed angiogenesis. However, the trouble with this type of inhibitors is that they work poorly in high growth factor concentrations, when the growth factor easily outcompetes the inhibitor. Also the delivery of drugs into tumors is hampered by erratic blood flow and high tumor pressure, which may prevent sufficient amounts of the inhibitor from reaching its target within the tumor.

The novel type of VEGFR-3 blocking antibody has an unprecedented mechanism of action, which was effective even at very high concentrations of the VEGF-C growth factor. Importantly, the authors showed that combined use of antibodies blocking growth factor binding VEGFR-3 dimerization provided not only an additive, but rather a synergistic inhibition.

"The new dimerization inhibitor unveils a biologically meaningful rationale for suppressing angiogenesis in tumors that could outperform traditional competitive inhibitors of angiogenesis in tumor therapy. These findings should translate into improved anti-angiogenic and anti-lymphangiogenic tumor therapies", says Professor Alitalo.