Tumor microenvironment and Angiogenesis as target for therapy and cancer prevention

Adriana Albini
Department of Medicine and Surgery, Milan-Bicocca University, Monza, Italy
IRCCS MultiMedica Science and Technology Pole, Milan, Italy

Angiogenesis is a necessary process for solid tumor survival, growth and dissemination, and has become a successful target in cancer therapy since 2004. It can be potentially targeted and in prevention, a concept we named as angioprevention. A complex microenvironment is cooperating with tumor and endothelial cells to promote malignancy. We sought to identify molecules and pathways to treat or prevent tumor development by targeting the microenvironment and inflammatory angiogenesis. We have shown that various chemopreventive molecules, such as flavonoids, antioxidants and retinoids, act on angiogenesis and tumor microenvironment, inhibiting the recruitment and/or activation of endothelial, innate immune and cancer cells[1].

Flavonoids suppressed the IkB/NF-kB signalling pathway suggesting that anti-oxidant compounds may also have anti-inflammatory effects. Triterpenoid derivatives (CDDO), fenretinide (4-HPR) and the beer hop isoflavone Xanthohumol are also strongly angiogenic. We have generated novel modified Xanthohumol formulations with increased efficacy in tumor prevention. Recently, we found that 4-HPR induces apoptotic cell death and necrosis in medulloblastoma cells and stem cells by activating procaspase-8 and -9. Endothelial and tumour cells are not the only possible target for antiangiogenic therapy or angioprevention. It is evident from a growing literature that native immune cells recruited into tumors in turn stimulate the endothelium and are responsible for an indirect pathway of tumor vascularization. Inflammation-dependent angiogenesis seems to be a central force in tumor growth and expansion, a concept supported by the observation that the use of "classic" anti-inflammatory drugs, such as non steroidal anti-inflammatory drugs, leads to angiogenesis inhibition. The mechanisms of inflammatory angiogenesis provide new approaches to prevent tumor angiogenesis by treatment with synthetic or natural agents with anti-inflammatory properties. We have recently isolated a novel population of pro-angiogenic natural killer NK cells associated with tumors, in particular lung and colorectal. Our data strongly support the concept that prevention-based approaches could focus on inhibition of angiogenesis and inflammation, both closely tied to tumour insurgence and progression, and confirm that angiogenesis and the tumor microenvironment represent a wide, but compelling, target for cancer prevention