

## **Signal amplification by tumor cells: clue to the understanding of the antitumor effects of cold atmospheric plasma and plasma-activated medium**

Georg Bauer

Institute of Virology, University Medical Center, Freiburg, Germany

Generation of extracellular superoxide anions by membrane-associated NADPH oxidase-1 (NOX1) is a hallmark of malignant transformation, as it stimulates proliferation and maintains the transformed state. However, NOX1-derived extracellular superoxide anions also drive two reactive oxygen species/reactive nitrogen species (ROS/RNS)-dependent intercellular apoptosis-inducing signaling pathways. These are the HOCl and the NO/peroxynitrite signaling pathway which activate the mitochondrial pathway of apoptosis and lead to the elimination of transformed cells.

During tumor progression, tumor cells regularly acquire resistance towards ROS/RNS-dependent intercellular apoptosis-inducing signaling. Their resistance is based on the expression of membrane-associated catalase which interferes with HOCl signaling through decomposition of  $H_2O_2$ , and with NO/peroxynitrite signaling through oxidation of NO and decomposition of peroxynitrite. The expression of comodulatory membrane-associated SOD on tumor cells is required to avoid superoxide anion-mediated inhibition of catalase.

Membrane-associated catalase and SOD of tumor cells represent a novel and specific target for rational tumor therapy. An analytical approach, based on experimentally-determined responses of cells from distinct steps of oncogenesis towards defined reactive oxygen/nitrogen species (ROS/RNS) is presented. It is suggested that low concentrations of singlet oxygen from cold atmospheric plasma (CAP) or generated by plasma-activated medium (PAM) cause local inactivation of tumor cell protective catalase. This allows for the generation of high concentrations of cell-derived secondary singlet oxygen, further inactivation of catalase and reactivation of ROS/RNS-dependent apoptosis-inducing signaling.

The understanding of this mechanism of signal autoamplification by tumor cells might be useful i) to define optimal dose and composition of CAP for tumor therapy, ii) to elucidate selective CAP and PAM action, iii) to allow for the establishment of valuable synergistic effects, and iv) to connect CAP and PAM-related ROS/RNS effects with immunogenic cell death.