Reactive Oxygen Species-mediated Intercellular Signaling of Malignant Cells: Control of multistep oncogenesis and a chance for novel therapeutic approaches.

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Abstract
Reactive oxygen species (ROS) exhibit procarcinogenic effects at multiple stages during multistep oncogenesis. As a hallmark of the transformed state, extracellular superoxide anions generated by NADPH oxidase1 (NOX1) are centrally involved in the control of the transformed state. These pro-carcinogenic effects of ROS are counterbalanced by specific ROS-dependent apoptosis induction in malignant cells, based on four interconnected signaling pathways. Thereby the HOCl and the NO/peroxynitrite signaling pathway are of major importance. Tumor progression selects for a phenotype characterized by resistance to ROS-dependent apoptotic signaling. Resistance is based on expression of membrane-associated catalase in tumor cells, which therefore represents a promising and unique target for specific tumor therapy. Novel approaches developed in vitro utilize antibody-mediated inhibition of catalase or ROS-driven singlet oxygen generation and subsequent inactivation of tumor cell catalase as initial steps. As a consecutive step, malignant cell-generated superoxide anions then drive apoptotic signaling with high selectivity for malignant cells. We propose to translate this complex but well-established ROS-dependent signaling chemistry into novel approaches for experimental therapy in vivo.

Selected Reference
Versatile Mechanisms of HCV to Modify Host Function to Maintain Inflammatory State

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Abstract
Hepatitis C virus (HCV) can cause chronic liver disease, which can progress to fibrosis, cirrhosis and hepatocellular carcinoma. Continuous activation of inflammation during persistent infection of HCV increases the risk of the development of carcinoma. HCV activates innate immunity such as TLR3 and RIG signaling upon infection. But HCV protease cleaves some adaptor proteins involved in these signaling and may allow virus to replicate persistently. HCV activates lipid metabolism. Accumulation of lipid droplets is triggered by activation of SREBPs by HCV Core proteins or by PANP mediated activation of IKKalpha. HCV Core protein produces ROS and excess activation of lipid metabolism also produces oxygen radicals. These radicals trigger production of various proinflammatory cytokines and chemokines, which contributes to persist inflammation. Besides the role of ROS, HCV proteins activate production of various cytokines via activating cellular factors such as STATs and NFkB. Another mechanism to activate proinflammatory cytokines is through the cross talk between HCV infected cells and hepatic stellate cells (HSC). We found that HSCs stimulated HCV-infected hepatocytes, leading to the expression of proinflammatory cytokines and chemokines. This effect was mediated at least by IL-1α, which was secreted by HSCs. The cross-talk between HSCs and HCV-infected hepatocytes is a key feature of inflammation-mediated, HCV-related diseases.

Selected Reference