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The ROS-producing anti-malaria drug dihydroartemisinine interferes with tumor cell metabolism and survival in normoxia and hypoxia

Sina Bader[1], Justine Rudner[2]
[1]***Institut für Zellbiologie (Tumorforschung), Essen, Germany***
[2]***Institut für Zellbiologie (Tumorforschung) , Essen, Germany***

Purpose: Hypoxia is one major factor responsible for poor response to chemo- and radiotherapy. It is highly heterogeneous, ranging from mild to severe hypoxia and also highly dynamic with respect to its duration. Moreover, tumor hypoxia fluctuates regionally as a result of the instability and chaotic organization of the tumor vasculature. In addition, fluctuating oxygen concentrations foster reprogramming of cell metabolism which helps tumor cells to adapt to the altered bioenergetic, biosynthetic and redox demands, resulting in resistance to standard therapies. Here, we investigate whether the ROS-producing anti-malaria drug dihydroartemisinine (DHA) can further boost oxidative stress induced by ionizing radiation (IR). Therefore we first analyze effects in normoxia (Nx) and acute hypoxia (Hx) and second in hypoxia-selected (hs) cells.

Methods: The effect of DHA, either alone or in combination with IR on acute and long-term cell death was measured in colon cancer and hs as well as non-selected (ns) lung cancer cells in Nx and Hx by flow cytometry and colony formation. Changes in gene expression were analyzed using gene array qRT-PCR and verified on protein level by western blot. We used a glutathione assay, measured ROS-production with cells overexpressing an oxidation-sensitive sensor protein targeted to mitochondria (MitoTimer) and examined changes in cell metabolism with Seahorse analyzer.

Results: DHA induces cell death in colon cancer and hs lung cancer cells especially under normoxic conditions. Moreover, cytotoxicity of IR could be increased by co-treatment with DHA in Nx as well as Hx. In both cells lines the inhibitory effects of IR on clonogenic survival could be enhanced with DHA under both conditions. Single treatment with DHA reduced long-term survival in colon cancer cells even stronger in hypoxia. DHA triggered oxidative stress responses, such as the transsulfuration and serine synthesis pathway predominantly under normoxic conditions. In colon cancer cells preliminary work showed an upregulation of glutathione synthesis in normoxia but not in hypoxia, which could result in a faster neutralization and an improved dealing with reactive oxygen species induced by DHA in normoxia. Moreover, DHA induced oxidative stress at the mitochondria and affected mitochondrial function, leading to decreased oxidative respiration and dissipation of the mitochondrial membrane potential.

Conclusion: DHA is a promising drug interfering with tumor cell metabolism and tumor cell survival in normoxia and acute hypoxia.