Role of Carbonyl Reductase 1 in Human Cancers

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Human carbonyl reductase 1 (CBR1) is a ubiquitous NADPH dependent enzyme belonging to the short chain dehydrogenase/reductase (SDR) family. It consists of 277 amino acid residues and catalyzes a large number of biologically and pharmacologically active substrates, including a variety of endogenous and xenobiotic carbonyl compounds [1]. CBR1 inactivates highly reactive lipid aldehydes, such as 4-oxonon-2-enal (ONE), which are able to modify protein and DNA [2]. Since tumor cells are under oxidative stress in hypoxic conditions, we first tested if CBR1 is upregulated by hypoxia inducible factor (HIF)-1α, helps tumor growth under hypoxia, and renders chemo-resistance to cisplatin and doxorubicin using hepatocellular carcinoma (HCC) cells. Also, we tested if CBR1 reduces doxorubicine (DOX) to doxorubicinol (DOXOL), which has less potent anti-cancer effects than DOX and leads to chronic cardiotoxicity, and if combination of DOX with CBR1 inhibition can enhance chemotherapeutic efficacy. In addition, we tested if CBR1 contributes to the low efficacy of arsenic trioxide (As2O3) which is used as an effective chemotherapeutic agent for acute promyelocytic leukemia (APL). Our results showed that CBR1 upregulated by HIF-1 α and other transcription factors contributes to tumor cell growth and chemo-resistance and Dox-induced cardiotoxicity. Therefore, we concluded that CBR1 is a good molecular target for the development of anticancer drugs for solid and leukemic cancers