Heme Oxygenase-1 in Tumors: Therapeutic Implications

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Heme oxygenase-1 (HO-1) is a stress-inducible enzyme degrading heme to iron, carbon monoxide and biliverdin, which is subsequently converted to bilirubin by biliverdin reductase. Recent evidence indicates that the functions of HO-1 extend much beyond the heme removal. Indeed HO-1 byproducts protect cells from damaging effects of oxidative stress, decreasing production of inflammatory cytokines, adhesion molecules, inhibiting the immune response, regulating the cell cycle and preventing neuronal and endothelial cells apoptosis. HO-1 is also involved in blood vessel formation, influencing the production of angiogenic cytokines and mediating the angiogenic activity of endothelial cells. Those beneficial properties are exploited for application in the treatment of cardiovascular diseases. However, effects of HO-1 activity may become detrimental in conditions when formation of new blood vessels may aggravate the disease and when attenuation of oxidative stress may diminish the effectiveness of therapy. Therefore, the investigations on the role of HO-1 in tumor-host interactions and anti-tumor therapy may add to better understanding of the mechanisms of tumor growth, angigenesis and resistance to therapy.

Data indicate that angiogenic properties of various cells types, including their propensity to produce vascular endothelial growth factor (VEGF), the major angiogenic mediator, are enhanced by pharmacological or genetic HO-1 overexpression. B16(F10) melanoma cells overexpressing HO-1 proliferated faster than wild type cells, and the vasculature in tumors growing from such cells was enhanced in comparison to wild type melanoma. Moreover, the expression of inflammatory cytokines was decreased in HO-1 overexpressing melanoma and the survival of mice with such tumors was shorter than those harboring the wild type. Interestingly, in mouse C-26 adenocarcinoma overexpression of HO-1 prevented the effectiveness of photodynamic therapy, and, accordingly, inhibition of HO activity increased the effectiveness of therapy.

Our data indicate that HO-1 overexpression may promote tumor growth, enhancing tumor cell proliferation, production of angiogenic mediators and blood vessel formation. Moreover, data

suggest, that due to inhibition of inflammatory response and protection against oxidative stress HO-1 may attenuate the effectiveness of anti-cancer therapy. Therefore, inhibition of HO-1 expression and activity may be considered as additional therapeutic approach in treatment of cancer and other angiogenic-dependent diseases. (The work is supported by research grants from Ministry for Scientific Research.)

References:

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