INVOLVEMENT OF PERIPHERAL BENZODIAZEPINE RECEPTOR (PBR) IN TUMORAL CELL PROLIFERATION AND ROS MODULATION

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The cell growth machinery is a very complicated and fascinating biological event. The balance between the biological pathways involved in cell death, such as apoptosis and cell proliferation, are linked to preserve life in a dynamic fashion. The deregulation of such genetic programmes may lead to different degenerative disorder. Peripheral benzodiazepine receptor (PBR) is ubiquitously expressed in all body cells with a particularly high abundance in steroid-producing tissues. PBR is involved in numerous biological functions, including steroid biosynthesis, mitochondrial oxidative phosphorilation and cell proliferation. Recent studies suggest a role of PBR in breast cancer cell proliferation, where the receptor has been linked to growing aggressive potential of the tumor cells *in vitro* and *in vivo*. In addition, PBR activation or inhibition seems to play an important role in ROS generation and thereby in the modulation of cellular death. Although it is now clear that proliferation of cells alone does not cause cancer, sustained cell proliferation in an environment rich in inflammatory cells, growth factors, and DNA-damage-promoting agents, certainly potentiates and/or promotes neoplastic risk. In such environment, proliferating cells that sustain DNA-damage and/or mutagenic assault continue to proliferate giving rise to cancer. Our results performed in different hepatoma cell lines indicate that the subcellular localization of PBR may play a role in the modulation of cell progression. In fact, nuclear PBR density correlates inversely with cell doubling time, as higher is the PBR expression as faster is the cell proliferation. Moreover analysis of PBR in six cases of hepatocellular carcinoma (HCC) resection confirm the data obtained *in vitro*. Numerous observations indicate that PBR partecipates in the regulation of apoptosis, i.e. overexpression of PBR attenuates apoptosis induced by oxygen radicals or ultraviolet light, various PBR ligands with nanomolar affinity for the receptor, such as Ro 5-4864 and PK 11195, modulate cancer cell response to apoptosis inducing signals. In this contest, we evaluated also the effect of administration of menadione a super-oxide inducer in hepatoma cell line in presence or not of micromolar concentration of PK 11195. Our results showed that the specific ligand was able to increase the effect of the menadione after 24 h of treatment. Moreover, preliminary results on the knockdown of PBR in the studied cell line seem to reinforce the idea of a direct involvement of the receptor complex in cell proliferation and survival.