Novel polyphenolic ligand of BP-Cx family drugs: cell distribution and mechanism of action

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BP-Cx-1, novel polyphenolic ligand, is a water-soluble fraction of wood lignin and is the platform for a portfolio of innovative pharmacological products such as antineoplastic agent BP-C1, radiomitigator BP-C2 and geroprotective composition BP-C3 [1]. In our previous study, a number of polyphenolic components of BP-Cx-1 (flavonoids, sapogenins, phenathrenes etc.) were identified as the major carriers of biological activity of BP-Cx drug family. *In vitro* and *in silico* target screening yielded overlapping lists of target proteins: adenosine receptors A1, A2A; dopamine receptor DRD4; glucocorticoid receptor GR; serotonin receptor 5-HT1; prostaglandin receptors PGI2, EP2; muscarinic cholinergic receptor, GABAA receptor [2]. Most of them are involved in cancer and/or inflammation signaling pathways.

In the present study, the IC50 of BP-Cx-1 was measured by radioligand method and a range of IC50 values between 22.8 and 40.3 μg/ml were obtained for A1, A2A, BZD, EP2 and IP (PGI2) receptors. IC50 for 5-HT1 and for GR were 3.0 μg/ml and 12.6 μg/ml, respectively, both being within the range of BP-Cx-1 concentrations detectable in *in vivo* models (see *Panchenko et al* abstract in this conference book).

Further, distribution of [3H] labelled BP-Cx-1 in murine fibroblasts NIH3T3 and MCF7/R carcinoma cells was studied by autoradiography method. [3H]-BP-Cx-1 (marked by silver grains formed under tritium β-irradiation) was mainly localized along the cell membrane, in the perinuclear region and in the nucleus, suggesting ability of BP-Cx-1 to penetrate cells and bind to membrane or cytosol receptors. It is hypothesized that [3H]-BP-Cx-1 detectable in the nucleus is part of an activated GR complex, known to be involved in regulation of transcription of genes responsible for the anti-inflammatory response.

It is reported, that glucocorticoids may act at the very first step of the immune response by modulating differentiation, maturation and function of dendritic cells (DCs) [3]. In our experiment, we observed similar effect of BP-Cx-1 on DCs: downregulation of expression of the lipid-presentation molecule CD1a, co-stimulatory molecules CD80, CD86 and CD 40, decreased production of pro-inflammatory cytokines IL-4 and TNFa and increased production of anti-inflammatory cytokine IL-10. Observed production of G-CSF and GM-CSF by DCs in response to treatment with BP-Cx-1 may explain the radiomitigating effect of BP-C2.

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