The purine cycle and its function in the regulation of purine compounds and prodrugs metabolism

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The purine cycle is composed by enzymes involved in the degradation of AMP, IMP and GMP such as cytosolic 5'nucleotidases, converting them in the correspondent nucleosides, a phosphorolytic cleavage for inosine and guanosine (a previous deamination for adenosine) and a base salvage through hypoxanthine guanine phosphoribosyl transferase (1,2). This cycle regulates the intracellular concentration of purine nucleotides, the phosphorylated ribose and PRPP. The rate of the cycle depends on the activity of the allosterically regulated nucleotidase involved (3).
Among the members of the 5'-nucleotidase family, there is only one membrane-bound ectosolic isoenzyme. This esterase prefers AMP as substrate but can hydrolyze a number of purine and pyrimidine phosphorylated compounds, indicating that no evolutive pressure to develop a more restricted specificity was exerted on this enzyme. On the contrary, five cytosolic isoforms have been evolved, probably by convergent evolution, showing different and restricted substrate specificity. The different isoforms have different level of expression and distribution in organs of vertebrates (4,5). The cytosolic nucleotidase specific for IMP and GMP (cN-II), is an enzyme allosterically regulated, structurally strongly conserved and expressed at a low but constant level in all organs and tissues in vertebrates (6). As far as we know, alteration of cN-II expression is limited to pathological conditions such as neurological disorders and cancer (7). Presently, we report the results of the modulation of cN-II specific activity exerted by silencing or hyperexpression in different cell types, and its effect on the purine cycle, in the attempt to better understand its role and implications in pathology and therapy. Furthermore, we propose that some of the enzyme involved in the intracellular metabolism and recycling of purine nucleotides are also present outside cells. The knowledge of the intracellular and extracellular metabolisms of purine compounds and their interplay is fundamental for the understanding of the purinergic signalling in particular in glyal and neuronal cells. Furthermore, the same enzymes involved in purine metabolism and recycling are also responsible for activation and inactivation of purine prodrugs and therefore for the determination of a successful therapy.

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