Perturbation of Intracellular Purine Nucleotides Balance as Effective Strategy for Cancer Therapy

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It is entirely accepted that a metabolic change in purine nucleotide concentration occurs during carcinogenesis which facilitate the pathological process of malignant cells such as proliferation, invasion and metastasis. Nucleotides participate in many biochemical processes as activated precursors and source of energy in nucleic acid biosynthesis and as intermediate products for synthesis of lipids and proteins. However, currently it has been documented that purine nucleotides act as signaling molecules which directly or indirectly regulate stability, subcellular localization and activation of plethora of proteins in cells. Although biosynthesis of purine nucleotides is up-regulated in malignant versus normal cells, the ratio of [ATP] and [GTP] is maintained constant about 7 to 1, which is critical for cell biological process. This biological fact makes GTP as rate limiting factor not only in nucleic acid synthesis but also in regulation of survival and death signaling molecules whose functions are regulated by GTP content. In this line, several strategies were developed that impact on intracellular GTP content and disrupt the ratio of [ATP]/[GTP]. For instance, inhibitors have been introduced in which some of them are in clinical trial at phase I and II, targeted edinosine 5’-monophosphate dehydrogenase (IMPDH) (type II) as rate limiting enzyme in GTP biosynthesis pathways in malignant cells. Mycophenolic acid, the most potent and selective IMPDH inhibitor, by depletion of intracellular GTP content disrupts purine nucleotides balance and conducts tumor cells toward apoptosis. On the other hands it has been ascertained that extracellular purine nucleotides, themselves act as signaling molecules which uptake by tumor cells through transporters on plasma membrane. In that respect, it has been disclosed that uptake of extracellular GTP by tumor cells leading perturbation of intracellular purine nucleotides balance which impact on signaling molecules and tilt cell’s fate toward apoptosis. From therapeutic standpoint, modulation of intracellular purine nucleotides by extracellular nucleotides or by selective inhibitors which target rate limiting enzymes in nucleotides biosynthesis pathways could be considered as a potential therapeutic option for malignant cells.

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