

Prostaglandins and the Role of MRP-4 Transporters in their Fate

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ABSTRACT

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Prostaglandins: Biosynthesis, Functions and Mechanism of Action

Prostaglandins (PGs) are synthesized by cyclooxygenases (COX-1, -2 and recently identified COX-3) from arachidonic acid after liberation of it by phospholipase A2 from membrane phospholipids and converted firstly into PGH₂ and then into different end products of prostaglandins including PGE₂, PGF₂ α . Their catabolism take place mostly by PG 15-dehydrogenase that oxidize them into biologically inactive metabolites such as 15-ketoPGE₂ [1]. It has been documented that the type of PGs in various organs is tissue-dependent as TXA₂ is synthesized dominantly in the platelets, while PGI₂ mostly is produced by the arterial wall, corpus luteum, follicle, and uterus and two others including PGE₂ and PGF₂a are produced in every organ [2]. Prostaglandins are involved in a large number of biological effects and their cellular actions are mediated by interaction of PGs with plasma membrane receptors. PG receptors belong to the superfamily of G-protein-coupled receptors with intracellular second messengers of cAMP, protein kinase C, and calcium [3]. Of course some prostaglandins interact with the nuclear hormone receptor peroxisomal proliferator-activated receptor γ [4].

PGs are not only important players in physiologic events such as renal and bronchial vasodilation, uterine smooth muscle relaxation and contraction and luteolysis, but also they do have crucial role in various pathologic conditions and disorders including: inflammation, pain, pyrexia, cardiovascular disease, renal disease, cancer, glaucoma, allergic rhinitis, asthma preterm labor, male sexual dysfunction and osteoporosis [5]. There are numerous reports showing downstream events following PGs binding to

extracellular domain of PG receptors, however based on current evidence still there are missing facts to show how PG are released.

Prostaglandins: Uptake and Release

An early opinion believes that PGs are impermeable to cell membranes and cannot cross plasma membranes by simple diffusion. The main reason for this phenomenon is that PGs are organic anions with a Pka of 5 and therefore at physiological pH (pH 7.4) they are as charged form [6]. Hence, to cross the cell membranes and consequently to bind the PG receptors for indigenously biosynthesized PGs, PGs need an aid of transporter systems (PG transporter). At the same time it is also believed that to launch the PGs degradation processes by 15-hydroxy PG dehydrogenase, the PGT-mediated uptake of PG from the extracellular environment is essentially needed [7]. During the last decades it has been explored that organic anion-transporting polypeptides (OATPs) are involved in transporting of PGs across the plasma membranes and among them OATP2A1/SLCO2A1 has been recognized as a solute and high affinity carrier for PG transporter. These transporters are acting via an exchange mechanism, with lactate acting as the counter-ion and playing a major role in the PGs disposition in vivo and also in the febrile response [8,9]. The release of prostaglandins, a process essential for their physiologic and pathologic effects, has not been fully discussed.

Based on early studies, it has been reported that the efflux of cAMP is inhibited by prostaglandins, suggesting their competition for the same transporters. Later investigations revealed that not only cAMP but also cGMP efflux is inhibited by some prostaglandins, too [10]. Very recently it has been demonstrated that Multiple

Drug Resistance-Associated Protein 4 (MRP4) along with PGT are important modulators of PGs signaling. Reid and co-workers (2003) as one of the leading research teams showed that MRP4 can release PGs from cells and even importantly inhibited from release of PGs by some nonsteroidal anti-inflammatory drugs [11]. In addition of previously mentioned indigenous compounds, MRP4 also functions in the absorption and secretion of drugs including antiviral, antibiotic, diuretic, antihypertensive, and cytotoxic agents, too [12]. This efflux transporter is expressed in wide range of tissues including in blood cells, smooth muscle cells, cardiomyocytes, bone cells, fibroblasts and cancer cells such as leukemia cell lines, lung cancer, pancreatic cancer and neuroblastoma and characterized by dual membrane localization [13].

The different membrane localization of MRP4 results in remarkable role in drug distribution and penetration. For instance, MRP4 localization at the brain blood barrier can prevent the penetration of oxins and xenobiotics into the brain. Accumulating evidence are indicating that the overexpression of MRP4 is one of the possible molecular mechanisms for failures of chemotherapy in certain tumors [14].

Conclusion

Taken all together, it is worth to direct some experimental studies to highlight the full role of PGT and MRP4 in the uptake and release of prostaglandins. It would be equally valuable to show how these transporter could be important therapeutic targets in various diseases, where PGs play crucial role in the pathogenesis of various diseases including cancers.

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