Editorial

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Cyclooxygenase and Prostaglandin in Cancer

Jong-Woo Kim
Department of Surgery, Bundang CHA Hospital, CHA University College of Medicine, Seongnam, Korea

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Inflammation, especially longstanding abnormal inflammation, seems to contribute to neoplastic transformation to some extent. We cannot help thinking of cyclooxygenase (Cox) and prostaglandin (PG) whenever we mention it. Three isoenzymes of Cox have been identified so far: Cox-1, Cox-2, and Cox-3, but Cox-3, recently identified, is a variant of Cox-1 and is also called Cox-1v. It is formed from a frame shift of the original Cox-1 gene, but it seems not to play usual Cox physiologic roles as in inflammation and fever, and it is still being studied [1, 2]. Although Cox-1 and Cox-2 enzymes basically work in the same way, they are expressed in different ways and at different levels in various organs and tissues. That is the reason side effects are different from selective inhibition against each enzyme. Cox-1, as a constitutional enzyme, is expressed from most cells in homeostatic processes and is inhibited in feedback. On the other hand, Cox-2 is mostly an enzyme that is induced under certain conditions such as inflammation or neoplastic process, but is rarely inhibited. Therefore, Cox-2 selective inhibitors effectively play their roles, especially at inflammatory sites, and do not damage the mucosa protection of gastric tissue without prohibiting the secretion of Cox-1, which is easily blocked by nonsteroidal antiinflammatory drugs (NSAIDs) in general. However, the selectivity of Cox-2 inhibitors does not seem to relieve other side effects of NSAIDs. Recently, increased risks of heart attack, cerebral stroke and renal failure have been reported with Cox-2 selective inhibitors, which seems to result from the reduced level of prostacyclin caused by Cox-2 inhibition. Prostacyclin has an important role in preventing platelets aggregation and blood clotting [3, 4].

Correspondence to: Jong-Woo Kim, M.D.
Department of Surgery, Bundang CHA Hospital, CHA University College of Medicine, 59 Yatap-ro, Bundang-gu, Seongnam 463-712, Korea
Tel: +82-31-780-5250, Fax: +82-31-780-5259
E-mail: kjw@cha.ac.kr

As we know, Cox converts arachidonic acid in the cell membrane to prostaglandin H2, the precursor of the final series-2 prostanoids such as PGE2, PGD2, PGF2, PGI2, and thromboxane A2. PGE2, one of the final products, is well known for its activities, such as softening the cervix, uterine contraction, inducing abortion, etc., in obstetric field [5]. However, the important thing is that PGE2 has recently been shown to have a strong relation with tumorigenesis in that it increases cell proliferation, angiogenesis and metastatic potential, and inhibits apoptosis and cellular immunity, which seem to be due to the increased expression of PGE2 by Cox-2 because excessive levels of PGE2 and Cox-2 are implicated in mediating several kinds of malignancies. However, we must also consider the Cox-2 activity in tumor tissue on its own without mediating prostaglandins. It can behave directly for tumorigenesis with activities similar to those mentioned above. For example, Cox-2 directly increases the intranuclear nuclear factor-kB, which is the main stimulus for gene activation and replication, and forms endogenous mutagen, malondialdehyde, from arachidonic acid, which can cause a mutation of p53, and stimulates vascular endothelial growth factor for angiogenesis [6, 7].

15-hydroxyprostaglandin dehydrogenase (15-PGDH) is supposed to degrade PGE2 selectively, and decreased expression of 15-PGDH might also be related with cancer as previously reported [8, 9]. As the author has mentioned, selective PGE2 inhibitors would work for the prevention or treatment of cancer if it developed. However, considering the direct effects of Cox-2 on carcinogenesis, cancer is unfortunately not that simple to get over. Therefore, selective PGE2 inhibitors will continue to be just one of many ordinary agents, but one that has a slight benefit in treating cancer. However numerous, these sorts of studies should form a basis for the future conquest of cancer.

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