EDITORIAL

COX-2 Inhibitors: A Potential Target for Drug Therapy in the Management of Colorectal Cancer

A R Albiruni Ryan*, A R Aireen Rosita*, A K Kamarul, MBBCh, A Qureshi, FRCSE(Gen)****

***Department of Biochemistry, Royal College of Surgeons in Ireland, Dublin, Ireland,**

****Department of Surgery, Hospital Universiti Kebangsaan Malaysia, Jalan Tenteram, Cheras, Kuala Lumpur**

Summary

Colorectal cancer is currently the third most common cancer in Malaysia. Elevated expression of COX-2, an induced cyclooxygenase isoenzyme, has been seen in colonic adenomas and colorectal carcinoma. There is evidence that inhibition of this COX-2 can decrease the risk of colorectal cancer. Selective COX-2 inhibitors may have a role in reducing the risk of colorectal cancer in high-risk individuals.

Introduction

The enzyme cyclooxygenase, better known as COX metabolises Arachidonic Acid into various prostaglandins[1]. Until recently, it was believed that COX was a single enzyme. However, in 1989 a second isoform of COX was discovered[2] and named COX-2. COX-1 is constitutively expressed in almost all cells in the human body. It has a role in normal physiological functions such as vascular homeostasis, renal osmoregulation and cytoprotection in the stomach[3]. In contrast, COX-2 is highly inducible and almost always absent in normal cell function. Elevated expression of COX-2 have been seen in arthritis, acute inflammation and has recently been recognised in epithelial malignancies such as colon carcinoma[4-6]. Non steroidal anti-inflammatory drugs (NSAIDs) form a drug group with anti-inflammatory, anti-pyretic and anti-thrombotic properties. They work by inhibiting the activities of COX, hence prohibiting the synthesis of prostanoids[7]. Drugs that preferentially or selectively inhibit the activity of COX-2 such as nimesulide, meloxicam and NS 398 have been proven to have a low IC-50 (inhibitory concentration to reduce biosynthesis by 50%) ratio for COX-2/COX-1 as opposed to non selective COX inhibitors such as asprin[8]. This means selective COX-2 drugs have less associated side effects as the activity of COX-1 still remains intact. The effects of NSAIDs on colonic diverticular disease are due to the non-selective inhibition of COX-1, and consequently an inhibition of the mucosal-protective prostaglandins. This in turn can predispose to colonic bleeding, more commonly associated with coexistent colonic diverticular disease.

Apoptosis or programmed cell death is a genetically controlled response for cells to commit suicide. The control of apoptosis is regulated by the bcl-2 gene[9]. In many neoplastic conditions, abnormality of function or expression of this family of genes has been demonstrated. On a cellular level, cell blebbing, pyknosis and DNA fragmentation in an apoptotic cell can be observed. Recently, it has been found that the use of NSAIDs can induce apoptosis in some forms of carcinomas, such as colon and rectal carcinoma, as well as in pre-malignant conditions such as polyposis coli[10,11].

Prostaglandins consist of a series of compounds collectively known as prostanoids. The compounds include both prostaglandins and thromboxanes. The generation of both prostaglandins and thromboxanes is initiated by the liberation of arachidonic acid from the cell membrane. Free arachidonic acid is converted by COX into prostaglandin H_2 (PGH_2). This compound is further metabolised into various prostaglandins depending on cell type. In platelets, Thromboxane A_2 (TXA_2) is produced while Prostaglandin E_2 (PGE_2) and Prostacyclin (PGI_2) are produced in monocytes and endothelial cells respectively[12]. The use of NSAIDs inhibits the activity COX and hence the production of prostaglandins and thromboxanes.

Expression of COX-2 and neoplasms

The expression of COX-2 in various types of neoplastic lesion is well recognised and documented. Elevated expression of COX-2 isoenzyme has been demonstrated in colon and rectal carcinoma, in HeLa cells and in pre-malignant conditions such as familial adenomatous polyposis and polyposis coli[13,14,15]. COX-2 expression is elevated in up to 85 - 90% of human colorectal carcinoma cases and in up to 40 - 50% of colonic adenomas[16]. In a recent publication, it was reported that cells with over expression of COX-2 demonstrated resistance to apoptosis with increased cell adhesion to extra cellular matrix, hence explaining the possible tumour genesis[17]. However, these effects were reversed with the administration of NSAIDs.

The use of inhibition of COX-2 and induction of apoptosis

This therapeutic aspect have been extensively studied in recent years. In 1991, a case controlled study reported that the use of NSAIDs reduced the risk of developing colon carcinoma by 50%[18]. In individuals with colorectal carcinoma, a similar (40 - 50%) decrease in terms of mortality was demonstrated with the administration of NSAIDs[19]. However, this protective effect does not seem to continue with cessation of therapy. The administration of sulindac, a selective COX-2 inhibitor not only brought the levels of COX-2 and prostaglandins formation to baseline but also restored normal levels of apoptosis[15]. Another study showed that administration of nimesulide, a selective COX-2 inhibitor, induced apoptosis in HeLa cells. The levels of cell death were comparable to that induced by cyclohexamide, a potent inducer of apoptosis[14]. In cases of familial adenomatous polyposis, the use of NSAIDs results not only in regression of the polypoid size, but also in the number of polyps[11].

However, how apoptosis is achieved in these studies still remains unclear. Some have postulated that NSAIDs actually induce tissue transglutaminases, a hallmark in apoptosis resulting in cytoskeletal crosslinking[10]. Cells in the G_0 phase are protected from cell death by p20 and other quiescence-specific proteins. The use of NSAIDs down regulates the expression of p20, an effect that enhances apoptosis[10]. There are also suggestions that COX-2 and local mediators may function in signal transduction pathways leading eventually to the ultimate goal of apoptosis, containing p53 and bcl-2 gene. However, a recent study suggested that apoptosis due to administration of NSAIDs involves a pathway that is independent of cyclooxygenase inhibition, cell cycle arrest and p53 induction[20]. Another paper has suggested that with the use of non-steroidals, the levels of arachidonic acid is elevated as the prostanoid biosynthesis is halted. This dramatic increase in arachidonic acid in turn stimulates the conversion of sphingomyelin into ceramide, a known mediator of apoptosis[21].

Conclusion

A number of malignant and pre-malignant conditions demonstrate over expression of COX-2. In these tumours or cell models, the use of non-steroidal anti-inflammatory agents can actually result in apoptosis, often with classical features. Although the exact mechanism by which apoptosis is achieved has yet to be determined, the significant decrease in terms of patient risk and mortality rate in cases of colon and colorectal carcinoma strongly indicates that specific/selective COX-2 inhibitors such as sulindac, meloxicam, NS 398 and nimesulide have a potential role in individuals with a high risk of colorectal carcinoma such as those with familial adenosis polyposis and those with a history of adenomas.

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