Comment: COX-2 and VEGF inhibitors could be considered as clinical treatment and prevention on the esophageal carcinoma

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Abstract

Cyclooxygenase (COX) and vascular endothelial growth factor (VEGF) play important roles in animals, especially in the carcinogenesis and the metastasis of the tumor. In the current issue of *Life Science Journal*, Xing *et al* offer the article of *Changes of COX-2 and VEGF expressions in esophageal precancerous and cancerous lesions from the patients at high incidence area in Henan province*. This article describes the expressions of COX-2 and VEGF in the patients with esophageal cancers and shows that the correlation between the expressions of COX-2 and VEGF was statistically significant. This suggests that COX-2 and VEGF play important roles in esophageal carcinogenesis and may be potential molecular targets for the esophageal prevention and treatment. [Life Science Journal. 2007; 4(2): 8 – 10] (ISSN: 1097 – 8135).

Keywords: cancer; cyclooxygenase; esophageal; VEGF

In the article *Changes of COX-2 and VEGF expressions in esophageal precancerous and cancerous lesions from the patients at high incidence area in Henan province* in this issue of *Life Science Journal*, Xing *et al*[1] analyzed the changes and clinical significance of cyclooxygenase-2 (COX-2) and vascular endothelial growth factor (VEGF) in esophageal precancerous and cancerous lesions from the 135 patients at Linzhou, Henan, China, a well-known region for its high prevalence of esophageal cancer, using the histopathological and immunohistochemical techniques[1]. They got the results showing that immunoreactivity of COX-2 and VEGF in severe esophageal dysplasia and squamous cell carcinoma was significantly higher than in other tissues, and the correlation between COX-2 and VEGF was statistically significant. They concluded that COX-2 and VEGF expressions are up-regulated in severe dysplasia and squamous cell carcinoma, suggesting that COX-2 and VEGF may play important roles in esophageal carcinogenesis and may be potential molecular targets for high risk subject screening, and early detection. From the results of this paper it can get the potential hypothesis that the selective COX-2 and VEGF inhibitors or the combined usage of the COX-2 and VEGF inhibitors could be considered as clinical treatment and prevention on the esophageal carcinoma.

VEGF-C is a new member of the VEGF family. According to the report by Zhang *et al*[2], there was a significant difference between the expression of VEGF-C in lymph node group and group without lymph node metastasis, and the expression of VEGF-C protein level was significantly higher in group with lymph node metastasia than in group without lymph node metastasis. There is a close correlation between VEGF-C expression and lymph node metastasis, and VEGF-C may be served as a useful prognostic factor in human esophageal squamous cell carcinoma[2].

COX is an enzyme playing important role in the formation of prostanoids. There are two different COXs in animals, COX-1 and COX-2. COX-1 is expressed in many different cells to create prostaglandins as basic housekeeping messages throughout the body. COX-2 is an inducible enzyme only in special cells and is used for signaling pain and inflammation[3]. The inhibition of COX could relieve the symptoms of inflammation and pain, such as the function of drugs aspirin and ibuprofen. Aspirin has potential function in the prevention or treatment

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of esophageal cancer, but its mechanism of action is still not clear. Aspirin attacks both COX-1 and COX-2. When COX-1 is targeted, the drugs can lead to unpleasant complications, such as stomach bleeding[4].

As a kind of lipids, thromboxane is produced in platelets by thromboxane synthetase, from the endoperoxides by the COX from arachidonic acid. Thromboxane is a vasoconstrictor, potent hypertensive agent, and facilitates the clumping of platelets. It is in homeostatic balance in the circulatory system with prostacyclin. Aspirin also acts by inhibiting the ability of the COX enzyme to synthesize the precursors of thromboxane within platelets. Thromboxane is named for its role in clot formation (thrombosis). Thromboxane A2 produced by activated platelets has prothrombotic properties by stimulating activation of new platelets as well as increased platelet aggregation. The latter is achieved by mediating expression of the glycoprotein complex GP IIb/IIIa in the cell membrane of platelets. Circulating fibrinogen binds these receptors on adjacent platelets, further strengthening the clot. It is believed that the vasoconstriction caused by thromboxanes plays a role in Prinzmetal angina[5]. Cancer growth is influenced by the environmental nutrition supply and one of the possible function of COX on cancer formation is through the thromboxane synthesis to infulence the circulation system.

VEGF is a substance made by cells that stimulates new blood vessel formation, a mitogen for vascular endothelial cells, and it is a polypeptide structurally related to platelet-derived growth factor (PDGF). VEGF is an important signal protein involved in angiogenesis. VEGF belongs to PDGF superfamily and has more than 10 isoforms, ranging in weight from 35 to 44 kDa. VEGF production can be induced in cells that are under hypoxia condition. When a cell is deficient in oxygen, it produces a transcription factor – hypoxia inducible factors (HIF). HIF stimulates the release of VEGF. Circulating VEGF then binds to VEGF receptors on endothelial cells, triggering a tyrosine kinase pathway causing angiogenesis. VEGF has been implicated with poor prognosis in breast cancer. The overexpression of VEGF may be an early step in the process of metastasis, a step that is involved in the "angiogenic" switch. Once released, VEGF may cause several responses eliciting a cell to survive, move, or further differentiate. VEGF is a potential target for the treatment of cancer. Although VEGF has been correlated with poor survival, its exact mechanism of action in the progression of tumors remains unclear[6]. COX-2 expression is strongly correlated with VEGF expression[7]. Genetic variants in COX-2 may play a role in mediating susceptibility to esophageal cancer[8].

According to the report by Kulke *et al* in 2004, preoperative chemotherapy and radiation induced expression of COX-2 in stromal cells and induced VEGF expression in both tumor and stromal cells. Pretreatment VEGF expression did not correlate with treatment response, and COX-2 expression correlated with treatment response only in the subset of patients with squamous cell carcinoma. Kulke *et al* concluded that neither COX-2 nor VEGF is strong predictors of treatment response and survival in patients undergoing preoperative chemoradiation for esophageal cancer[9].

According to the report by Xi *et al*, median COX-2 mRNA expression levels were significantly different between paired tumor and normal tissues. Comparison of pre-therapeutic and posttherapeutic specimens showed a significant difference in COX-2 protein expression. High COX-2 protein expression in post-therapeutic resection specimens was significantly associated with minor histopathologic response and poor prognosis. High COX-2 protein expression following neoadjuvant radiochemotherapy in resection specimens is significantly associated with minor histopathologic response to neoadjuvant therapy and very poor prognosis[10].

As the reported by Okawa *et al*, heparanase and COX-2 exhibited a similar pattern in esophageal tumor tissues, and expressions of heparanase and COX-2 correlated with tumor malignancy and poor survival, and also revealed a significant correlation with high intratumoral microvessel density. Up-regulation of COX-2 mRNA and protein was observed in esophageal cancer cells transfected with heparanase cDNA. COX-2 promoter was activated after heparanase cDNA was transduced and the deletion/mutation of three transcription factor (cyclic AMP response element, nuclear factor-kappaB, and nuclear factor-interleukin-6) binding elements in COX-2 promoter strongly suppressed its activity. Depending on their research results, Okawa *et al* suggested that heparanase may play a novel role for COX-2-mediated tumor angiogenesis[11].

According to the studies by Yu *et al*, marked COX-2 expression was shown in squamous cell carcinoma and esophageal squamous dysplasia, and no marked COX-2 expression was observed in the normal squamous epithelium, respectively. NS-398 could inhibit esophageal cells growth in a dose-dependent manner, induce apoptosis, and elevate caspase-3 activity *in vitro*. These studies provided the evidence that COX-2 is upregulated in the majority of cases of squamous dysplasia and squamous cell carcinoma of esophagus, and that NS-398 can inhibit growth and induce apoptosis via activating caspase-3 activity *in vitro*. These results suggest that selective inhibitors of COX-2 may be an effective preventive and therapeutic option for esophageal carcinoma[12].

Beside the functions of COX and VEGF in esophageal precancerous and cancerous lesions, studies also showed

that uremic patient with the hemodialysis requirement had higher COX content. Uremic patients perform the derangement of the formation of thromboxane A2 and prostacyclin that is likely to be related to reverse inhibition of the function of platelet cyclooxygenase and lipoxygenase by plasma inhibitor. According to the studies by Rudko *et al* in 1991, the recovery of the platelet COX inhibition can be attained after adequate hemodialysis[13].

Many studies have been made on the biological roles of COX-2 and VEGF on the cancer and other diseases, and the exploring to find the inhibitors of COX-2 and VEGF on the cancer prevention and treatment is a critical topic in the clinical applications[14–17].

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