A linker Molecule for Regulating Inflammation and Angiogenesis

Jung-Ae Kim

College of Pharmacy, Yeungnam University, Gyeongsan, 712-749, Korea

Conventional nonsteroidal antiinflammatory drugs (NSAIDs) which are the most commonly prescribed drugs to treat inflammation has been under investigation for the possibility of a chemopreventive role since the late 1970's. Various experimental models of carcinogenesis have suggested that the effect of NSAIDs are related to the induction of apoptosis, inhibition of angiogenesis and metastasis, and the alterations in NO, VEGF and cyclooxygenase-2 (COX-2).

COX-2 is an inducible immediate early gene associated with inflammation, cell growth and differentiation, prevention of apoptosis and tumorigenesis. Over-expressed COX-2 has been considered to play a critical role in tumor promotion stage. In fact, in a variety of human cancers, upregulated COX-2 expression has been reported. COX-2 is also implicated in the angiogenesis of a variety of human malignancies. The tumor microenvironment is largely orchestrated by inflammatory cells such as which fully participate in the angiogenic process through secreting cytokines that may affect endothelial cell function. Endothelial cells, in turn, are involved in inflammatory cell extravasation underlying inflammation. Therefore, the COX-2 inhibitors which selectively regulating the production of cytokines in the inflammatory cells are the targets for managing both inflammation and angiogenesis, in turn, cancer.

Since conventional NSAIDs are used limitedly because of their damaging effects upon the stomach and kidneys at a dose that inhibits prostaglandin production, the selective COX-2 inhibitors are adopted to minimize the side effects of NSAIDs. However, they also have shown serious cardiovascular side effects. In the vascular endothelium, although COX-1 is constitutively expressed, COX-2 is the dominant producer of prostacyclin which inhibits platelet aggregation, prevents proliferation of vascular muscle cells, and promotes vasodilation. Endothelial COX-2 is upregulated by any type of stimulus such as shear stress. Concomitantly, platelet COX-1 produces enhanced TXA2 which exerts the exact opposite effects of prostacyclin. Selective COX-2 inhibitors suppress prostacyclin production while COX-1-derived TXA2 remains unaffected, which leads to a thrombotic response. Therefore, highly selective COX-2 inhibitors may not be the proper strategy to manage the inflammation and cancer angiogenesis in a long term basis.

Recently, the use of dual acting inhibitors of cyclooxygenases and lipoxygenase has been highlighted for their minimized side effects compared to NSAIDs. We found that the drug is also inhibiting angiogenesis and tumor growth, indicating that the dual acting inhibitor may be a good candidate for regulating inflammation and angiogenesis.