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Review Article

Oral cancer chemoprevention: COX-2 inhibitor a covenant

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ABSTRACT

Oral cancer survival remains poor despite advancement in treatment modalities. In oral cancer and oral premalignant lesions, cyclooxygenase-2 (COX-2) is widely expressed and tends to be enhanced especially in high-risk oral lesions. Numerous researches suggests that the inflammation pathway of cyclooxygenase/prostaglandin E2 (PGE2) leads to the development and progression of a number of cancers, including oral squamous cell carcinoma (OSCC). With an emphasis on research data, this article discusses the relationship between inflammation and cancer, summarizes the use of anti-inflammatory agents COX-2 inhibitors for cancer chemoprevention and treatment, and explains the mechanisms underlying the anti-cancer effects of anti-inflammatory agents (COX-2 inhibitors).

Keywords: COX-2 inhibitor; Inflammation, Oral cancer

INTRODUCTION

About 354,864 new cases of oral cancer are detected with 177,384 death annually worldwide.[1] Prognosis at the early stage of oral cancer is significantly better as compared to an advanced stage with metastasis.[2] Oral cancer is a morbid disease. The five-year survival rate is less than 50%. It is more prevalent in lower socioeconomic communities where tobacco habit is prevalent among people.[3] Numerous reviews have outlined interesting and fascinating evidence that nonsteroidal anti-inflammatory drugs (NSAIDs) have promise as anticancer drugs. It has been shown experimentally that nonsteroidal anti-inflammatory drugs stimulate apoptosis and inhibit angiogenesis, two mechanisms that help to suppress malignant transformation and tumor growth.[4-6] In present review, we have focused discussion on role of cyclooxygenase-2 inhibitors in oral cancer chemoprevention.

COX-2 INHIBITORS

COX-2 inhibitors are categories of NSAIDs which are generally used as analgesic, antipyretic and anti-inflammatory agents since a very long time. Recently found that these drugs can also be used for cancer prevention and treatment.[7,8] COX-2 inhibitors are isoforms of COX inhibitors. COX-2 enzymes are generally absent in normal tissue; however, they are extensively produced in inflammation and cancerous tissue. COX-2 inhibitors selectively target COX-2 and hence it produces much lower toxicity than the traditional NSAIDs.[8,9] Other advantages of using COX-2 inhibitors include easy application and relatively low cost through oral administration on an outpatient basis.[10] Studies confirmed that NSAIDs have a remarkable inhibitory effect on the growth of oral squamous cell carcinoma (OSCC). Treatment with NSAIDs instigate a remarkable dose and time dependent cell growth reduction

accompanied by an increase in apoptosis.[11] The exact mechanism of COX-2 inhibitors in cancer inhibition is not clearly understood but these COX-2 inhibitors have multiple mechanism of action in reducing carcinogenesis like upregulation of apoptosis, reduction in inflammation mediators, suppression of mutagens synthesis, inhibition of neo-angiogenesis.[4,12-14]

CANCER AND INFLAMMATION

Twenty percent of cancers are initiated by chronic inflammation or persistent infections.[15] Inflammation is a response of the body like a defence that is initiated because of any tissue injury of any nature via numerous releases of inflammatory mediators. Variety of inflammatory mediators like prostaglandins (PG), COX enzyme, matrix metalloproteinases (MMPs) and cytokines can lead to genetic and epigenetic alterations that can lead to alteration in tumor suppressor genes through post-translational modifications and DNA methylation.[16] Cancer cells can express cytokines that recruit neutrophils and macrophages.[17] These cells then release more inflammatory molecules that can lead to amplification of the inflammatory response. Tumor growth can also physically damage the normal tissue which in turn activates the production of damage-associated molecular patterns (DAMPs) that triggers resident granulocytes receptors and it initiates inflammation. The tumor growth can compress lymphatics and blood vessels leading to less nutrient and oxygen supply.[18,19] Tobacco smoke can cause cancer as it has the ability to cause chronic inflammation and production of reactive oxygen species (ROS).[20] Chronic inflammation is affected by variety of the factor's interleukins, nitrogen metabolites, oxygen and growth factors. Many factors not only induce the inflammation and repair, but can also lead to cancer concatenation.[21] COX-2 is expressed in OSCC and the surrounding lymphocytic infiltrates that points towards the fact that there is connection between inflammation and carcinogenesis.[22] Oral dysplastic lesions and OSCC has increased level of COX-2 as compared to the oral hyperplastic epithelium, pointing towards, COX-2 is involved in the early stages of oral carcinogenesis.[23] COX-2 is rarely expressed in normal epithelium but it is highly expressed in cancer and dysplastic cells.[24,25] Excessive expression of COX-2 in OSCC enhance the release of PGE2.[26] COX-2 is linked with OSCC metastases. COX-2 and PGE2 also cause enhance migration and upregulation of intercellular adhesion molecule-1 (ICAM-1) in the oral squamous cell carcinoma.[27]

Cyclooxygenase-2 also helps in prognosis of the OSCC.[28] Poor disease-free survival is seen in high expression of COX-2 level.[29] Role of inflammation in OSCC also supported by the finding of the study that showed benefit to cancer patients when anti-inflammatory medications have been combined with cancer therapy like combination of celecoxib with cetuximab cause reduction in migration and invasion of oral squamous cell carcinoma.[30]

COX-2 INHIBITORS IN CANCER PREVENTION

Cancer chemoprevention is the use of pharmacological agents to suppress, prevent or reverse the carcinogenesis process. COX-2 inhibitors have exhibited a potential role in various studies that it can help in the prevention of breast, skin, colon and other cancers.[13,31-33] COX-2 is connected in tumorigenesis in various tissues like head and neck tumors.[34] COX-2 is considered to contribute in carcinogenesis by inhibiting apoptosis, stimulating cell proliferation and enhancing angiogenesis.[35-37] That is why, cancer preventive and treatment strategies are using COX-2 inhibitors as potential medication.

COX-2 inhibitors cause reduction in the rate of growth of established tumors in preclinical studies.[38] Studies done on rats indicates that COX-2 inhibitors reduce the incidence and multiplicity of oral dysplasia and carcinomas. This shows the chemo-preventive ability of COX-2 inhibitors by inhibiting cell proliferation activity.[39,40] In a study done on cultured oral SCC cells, inhibitory effect on PGE2 production and growth of the carcinoma cell lines was found by COX-2 inhibitors.[41] A study on rat tongue cancer revealed that administration of NSAIDs reduced the incidence of squamous cell carcinoma in animals to 23-31% as to compared 71% in untreated controls.[42]

COX-2 overexpression leads to rise in the level of antiapoptotic protein bcl-2 that can lead to survival of damaged cells that is resistant to apoptosis and causing tumorigenesis.[43] A study done by Shiff et al showed that NSAIDs induce apoptosis in colon cancer.[44] Various studies showed a correlation between COX-2 level and angiogenesis with increased production of vascular-endothelial growth factor (VEGF).[45,46] VEGF level increased in progression from dysplasia to carcinoma.[47] The inhibition of COX cause decreased angiogenesis and reduced tumor invasiveness and metastasis.[48,49] In a nude mouse model of oral cancer COX-2 inhibitors have shown delay in cell growth and volume of tumor by reducing neo-angiogenesis.[50] That gives a proof of COX-2 inhibitors chemo-preventive action. COX-2 inhibitors may forestall carcinogenesis by influencing other non-COX, non-PG-related sub-molecular components.[51]

CONCLUSION

Various mechanism by which COX and PG add to carcinogenesis have been distinguished, including the restraint of apoptosis, modulation of inflammation and immunosuppression, expanded angiogenesis and invasion and transformation of procarcinogens to cancer-causing agents. COX-2 inhibitors, induce apoptosis, reduce cell proliferation, and inhibit angiogenesis helps in chemoprevention. Further research is needed in this subject.

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