**Letters to the Editor**

**Cyclooxygenase Inhibitor Ketorolac or Mast Cell Stabilizers: Immunologic Challenges in Cancer Therapy**

**To the Editor:** I have reviewed with interest the Featured Article by Mulshine et al. (1) reporting on the effects of a nonselective cyclooxygenase inhibitor, ketorolac tromethamine, as an oral rinse on oropharyngeal leukoplakia in randomized double-blind, placebo-controlled Phase II clinical trials. The study results confirmed the previous findings that the local delivery of the cyclooxygenase-containing oral rinse was well tolerated. In addition, they reported that the drug produced no significant reduction in the extent of leukoplakia over the placebo (a 20% alcohol-based solution). The authors suggested that the comparable favorable response rate to placebo arm may have been attributed to the improved oral hygiene through sustained twice-daily rinsing that could reduce the bacterial burden in the oral cavity and the down-regulation of inflammatory mediators (1). They further provided support for the placebo effects that others reported that rinsing with water produces such favorable response (1). The authors also suggested that oral cancer cells can make and respond to inflammatory mediators such as interleukin-6 and interleukin-8 (1).

The placebo effect (alcohol-based solution or water) in this and other studies cited by authors (1) is very interesting perhaps for more than the suggested reason of improved hygiene and the reduction of burden in bacterial-induced inflammation (1). Regular rinsing with water or alcohol-based solutions is very likely to dilute (wash away), to varying degrees, the preexisting cumulative and reactive components of chronic inflammatory responses including histamine, heparin, tryptase (or chymase), eotaxin, a variety of reactive oxygen or nitrogen species as well as the products of activated lipoxygenase and cyclooxygenase of membrane arachidonic acid metabolism [e.g., prostaglandin (PG) E2 (PGE2)] from the site of lesion. Persistent inflammatory responses and the presence of inflammatory mediators are likely to cause progressive worsening of the tissue lesions (e.g., development of leukoplakia in the oral cavity). Rinsing the areas of injuries is likely to wash away (reduce) the effect of mast cell mediators. A decrease in mediators effects [e.g., reduction in histamine binding to vascular receptors (H1 and/or H2)] could perhaps further limit activation of other vascular components (e.g., vascular endothelial growth factor) that will also limit the infiltration of inflammatory cells and mediators/cytokines (e.g., interleukin-6, interleukin-8, other growth factors, and PGs) to the site of injury. However, the possibility of spontaneous tissue healing in patients suffering from leukoplakia when inflammatory conditions are decreased may not be ruled out. Tissue lesions may be repaired through wound healing process as a normal function of tissue for a post-inflammatory event.

Mulshine et al. (1) suggested that the development of leukoplakia in the oral cavity or lung cancer (2) is due to the presence of chronic and recurrent inflammatory conditions that cause abnormal synthesis of PGs, particularly through activation of cyclooxygenase enzymes. Whereas the drug permeability problem/limitation into the site of lesion has been suggested as a reason for ineffectiveness of cyclooxygenase inhibitor in this (1) or perhaps other clinical studies, other factors may contribute to the ineffectiveness of inhibitors of cyclooxygenase-1 or cyclooxygenase-2 enzymes for improving cancerous or precancerous lesions.

Activation of cyclooxygenase enzymes (constitutive or inducible, cyclooxygenase-1 or cyclooxygenase-2) and production of prostanoids (e.g., prostacyclin/PGI2/PGF-1α or PGE2) may be considered secondary events during inflammatory/immune response processes (3, 4). In a series of studies we determined that the release of histamine from degranulation of mast cells was shown to be a primary event in the course of acute inflammatory responses followed by the release of prostanoids (e.g., prostacyclin or PGD2/PGF-1α) in an experimental model of allergy (3, 4). Alterations in the composition, ratios, or levels of mediator response were suggested to occur during the chronic inflammation by partially degranulated or “leaky” mast cells that could favor immune suppression pathways and production of PGE2 (3). Furthermore, degranulation of mast cells induces activation and metabolism of membrane arachidonic acid, which activates cyclooxygenase and lipoxygenase pathways with the production of PGs (e.g., PGE2) and leukotrienes (e.g., LTC4, LTD4, LTE4, by synthases; refs. 3–7). Therefore, inhibition of cyclooxygenase enzymes may exacerbate the activation of arachidonic acid metabolism through lipoxygenases pathways and production of vasoactive components such as leukotrienes by specific enzymes (e.g., LTC4 synthsase; ref. 6) as a feedback control mechanism.

Mast cells possess pleiotropic properties for cell growth arrest (apoptosis) as well as tumor growth promotion and angiogenesis (3, 7–10) whether they are considered mature (fully granulated) or partially granulated (3, 5, 8) and/or perhaps through phenotypic properties (9) and the extent of production of tryptase and/or chymase enzymes. Increase in mast cells and up-regulation of tumor angiogenesis in oral squamous cell carcinoma was suggested to be through mast cell release of tryptase (10). Down-regulation or a weak type 1 hypersensitivity response, due to a decrease in number of functional (mature or fully granulated) mast cells, was suggested to cause promotion of antigen entry into epithelial tissue and a basis for induction of massive hyperplasia of lymphoid tissues in an experimental model of allergy (3, 5). In these studies a low level of recurrence hypersensitivity response and the loss of functional mast cells correlated with the genesis of prominent follicular hyperplasia of the conjunctival-associated lymphoid tissues and extensive changes in epithelium accompanied by neovascularization (3, 5). Whereas in the hyperplastic lymphoid tissue many partially granulated mast cells were identified, the relative number of functional (mature) mast cells to hyperplastic
lymphoid cells decreased during the chronic phase of inflammation-induced development of tumor-like lesions in lymphoid tissues as well as in intermediate phase of inflammatory process (3, 5, 8). These results were supported by other reports that a decrease in the ratios of mast cells to tumor cells was correlated with reduced survival rates in patients with pulmonary adenocarcinoma (9). It is suggested that fully granulated mast cells are considered to possess tumoricidal properties whereas partially degranulated or “leaky” mast cells have tumor growth-promoting and angiogenic function.

In the design of drugs for treatment or prevention of cancer or precancerous lesions, it may be more beneficial to consider agents that stabilize, restore, or improve functionality of mast cells, or perhaps other cells in the innate immune system such as natural killer cells, dendritic cells, or macrophages (3). Focusing on the design of mast cell stabilizers, for example, using a combination of inhibitors of IgE-Fc receptor function, cromolyn derivatives, antihistamines, or inhibitors of heparin may prove to be a superior strategy for enhancing the tumoricidal role of mast cells, compared with using inhibitors of cyclooxygenases which are considered as the consequences of immune dysfunction including perhaps the loss of mast integrity and function. The design and use of suitable mast cell stabilizers is suggested to reduce mast cell “leakiness” and provide an opportunity for mast cells to mature (be granulated) for their tumoricidal properties (e.g., to increase the ratios of prostacyclin/PGI2/PGF-1α to PGE2), which could contribute to the improvement of the balance between the ratios of T-cell subtypes (Th1/Th2 cell) and immune function.

The current extensive research focusing on the molecular mechanisms of immune dysfunction and cytokine/chemokine biology brings hope and anticipation that better characterization of the dynamic and complex pathways in immune dysfunction in the process of tumorigenesis may not be out of reach. Because cancer is not a one disease, identifying the molecular entities involved at specific developmental phases of tumor should lead to better design of combination therapies (e.g., development of cytokine/chemokine chips tailored at specific points of dynamic phases of immune responses for a single disease entity; ref. 3). The proper outcomes should help not only for better diagnosis of cancer (suitable biomarkers), perhaps at earliest stages of development, but also for better designs of cytokine therapies according to particular characteristics of host-defense immune mechanisms at play.

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In Response: Two reasons support the use of a locally delivered pan cyclooxygenase inhibitor as we recently reported (1). The first is to reduce systemic drug exposure by limiting drug administration to the area of disease involvement. As we recently reviewed, this local delivery strategy has been successful in a variety of clinical settings (2). The appeal of this strategy, especially related to the cyclooxygenase drug target, has been underscored by the recent concerns surrounding the withdrawal of Vioxx (3, 4). The development of selective cyclooxygenase-2 inhibitors, such as Vioxx, represented another strategy to mitigate the gastric toxicity of inhibiting cyclooxygenase activity while preserving the therapeutic benefit of reducing cyclooxygenase activity in other parts of the body.

As suggested by Dr. Khatami’s letter, the precise basis of the favorable effects of nonsteroidal anti-inflammatory drugs on cancer progression is unclear (5, 6). Recent research lends conceptual support to the interesting mechanistic proposal of Dr. Khatami. However, this complexity of potential mechanisms highlights the second advantage of local versus systemic drug delivery (7). With local drug delivery, elucidating the mechanism of drug effect is less complicated than sorting out such issues with systemic drug delivery. Orally delivered drugs are subject to extensive enterohepatic metabolism and interactions with serum proteins resulting in both desired on-target and undesirable off-target effects. Undesirable off-target effects may be related to the action of drug metabolites not required for the desired drug effect and so direct epithelial drug delivery may mitigate this problem.

In saying this, our recent report did highlight that using locally delivered drug still presents distinct pharmacological challenges, such as with drug percolation, but these problems may be more
tractable than those with systemic management of a complex drug target like cyclooxygenase biology.

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