SEVERE INFLAMMATION IN ORAL LICHEN PLANUS MIGHT BE RESPONSIBLE FOR ITS CARCINOGENIC POTENCY

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The erosive form of oral lichen planus (OLP) shows apparently severe inflammation which is further confirmed from histological studies and from the overexpression of its inflammatory markers viz., NFkB, IL-6, TNF-a, COX-2 and iNOS. These characteristics in networked interaction with reactive oxygen or nitrogen species, inactivation of apoptosis or of death receptor pathways, as observed in cancerous condition, obviate OLP as a disease with tumorigenic potency.

Lichen planus is a well-established chronic inflammatory disease that affects the skin, oral and genital mucosa (Neville *et al*, 2009). The oral lesions are more common than the dermal lesions and also have the potentiality of malignant transformation to oral squamous cell carcinoma (OSCC), which may range from 0-12.5% (Gonzalez-Moles *et al*, 2008). It is a T-cell mediated autoimmune disease, where the auto-cytotoxic CD8+ T cells trigger the apoptosis of the basal cells of the oral epithelium (Ismail *et al,* 2007).

The inflammatory response is a coordination of various signalling pathways that regulates the expression of both pro- and anti-inflammatory genes in resident tissue cells and migrated leukocytes from the blood (Akira *et al,* 2006). Several studies reported that inflammatory cells can release mediators like cytokines, chemokines and metabolites of arachidonic acid, which helps in further infiltration of inflammatory cells to the damaged site, ultimately enhancing production of reactive oxygen species. These modulators can activate transcription factors like (nuclear factor-kB) NF-κB and mediate cellular stress response. Induction of cyclo-oxygenase-2 (COX-2), inducible nitric oxide synthase (iNOS) and expression of NF-κB dependent cytokines, viz., tumor necrosis factor-alpha (TNF-α), interlukin-6 (IL-6) which play a key role in oxidative stress induced inflammation (Hussain and Harris, 2007). Inflammation is a protective mechanism employed by tissues against endogenous and exogenous antigens. The relationship between chronic inflammation and many cancers have been recognized earlier. Here, the role of inflammatory markers like NFkB, IL-6, TNF-α, COX-2 and iNOS, in OLP pathophysiology, have been analyzed.

OLP is most commonly (>45%) found only in the buccal mucosa and 20% patients initially report with tongue or gingival lesions with inflammatory infiltration. The total count of WBC, lymphocytes and neutrophil counts as well as ESR level are significantly more than that of the normal subjects which may account for the immune system disorder or acute stress probably involved in the etiogenesis of OLP (Jana and Ghosh, 2014).

NF-kB is a transcription factor that regulates multiple cellular processes including cell growth, survival and division, apoptosis, stress, hypoxia and immune function. TNF-alpha is a NF-kappaB-dependent pro-inflammatory cytokine linking chronic inflammation and cancer by inducing neoplastic cellular phenotypes and angiogenesis. IL-6 is also a NF-kappaB-dependent pro-inflammatory cytokine, which participates in inflammatory and immune responses and sometimes promoting the rate of metastasis. COX-2 plays a key role in the occurrence and development of inflammation. Overexpression of COX-2 is implicated in tumour growth, invasion and metastasis, angiogenesis and inhibition of apoptosis, leading to the development of cancer. The iNOS is expressed in response to specific stimuli, such as endotoxin and cytokines leading to enhanced NO production for many hours without further stimulation. The expression of iNOS may be beneficial in host defence or in modulating the immune response. Chronic course of OLP may activate expression of NF-kB (Santoro *et al*, 2003), TNF-α, IL6, (Rhodus *et al*, 2005), COX-2 and iNOS in OLP patients

A hallmark for cancer progression is DNA damage, resulting either from various carcinogens accumulating from etiologic influences or due to genetic errors. Increased DNA fragmentation pattern was observed from OLP tissue genomic analysis compared to control group samples.

As inflammation is considered to be a major precursor for cancer development, primarily through the production of free radicals by inflammatory cytokines which are soluble mediators of intracellular communications, a plausible interaction leading to carcinogenicity has been outlined here. These cytokines contribute to a chemical signalling language that regulates development, tissue repair, hemopoiesis, inflammation and the specific and non-specific immune responses. Binding of cytokines to their receptors initiates transmission of extracellular information into the cytoplasm and the nucleus by various signalling pathways through NFkB or mitogen-activated protein kinase (MAPK) (Miyajima *et al*, 1992). Inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN- α have been shown to generate reactive oxygen species (ROS) in nonphagocytic cells too (Chapple, 1997). TNF- a enhances ROS production by neutrophils, while IL-1-ß, TNF-α, and IFN-μ stimulate the expression of inducible nitric oxide synthase (iNOS) in inflammatory and epithelial cells (Federico *et al* 2007). In animal models of multiple myeloma, plasma cells require IL-6 for growth, which is provided by macrophages in the chronically inflamed tissue (Dedera *et al*, 1996). IL-6 is stimulated by prostaglandin E2 derived from COX-2, which is elevated in inflammatory macrophages and can be inhibited by anti-inflammatory drugs (Hinson *et al,* 1996; Shacter *et al*, 1992).

After an inflammatory stimulus, initiation of carcinogenesis mediated by ROS may be direct (oxidation, nitration, halogenation of nuclear DNA, RNA, and lipids) or mediated by the signaling pathways activated by ROS. Nitric oxide is another free radical implicated in carcinogenesis, and is synthesized by iNOS, usually after challenge by immunological or inflammatory stimuli (Nathan & Xie, 1994; Davis *et al*, 2001). It is expressed only during inflammation and is induced by cytokines such as interferon-μ, TNF-α, IL-1, etc.

The ROS produced by cytokine induction can be an important signal for other biological effects in cells, such as proliferation and programmed cell death. Cancer results from proliferation of cell with damaged DNA, whereas, apoptosis causes activation of death

pathways and prevents unlimited proliferation of undesirable cells. The final fate of the damaged cell is a resultant if the tilting of the fine balance in favour of or against apoptosis of the cell with severe inflammation. As the above discussed characteristics of OLP well resemble that of carcinogenic condition, and there is about 2% propensity for its malignant transformation, it may be assigned "premalignant" tone.

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