

## **WHEN THERE'S SMOKE THERE'S.....CCN2**

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### **ABSTRACT**

**Smoking causes oral fibrosis. In a recent report, Takeuchi and colleagues (J Dent Res 89:34-9, 2010) evaluate whether nicotine can directly elevate collagen production in gingival fibroblasts. They show that CCN2 (connective tissue growth factor, CTGF) is elevated in response to nicotine and that a neutralizing CCN2 antibody reduces the ability of nicotine to promote collagen production. These data suggest that nicotine from smoking may promote periodontal fibrosis via CCN2. This commentary summarizes these findings.**

Many of the health issues involved with smoking are obvious and well-documented. Perhaps underappreciated is that fact that the oral cavity is one of the first areas of the body affected by smoking; smoking is a major contributing factor to periodontitis, for example (Calsina *et al.*, 2002). Interestingly, very few studies have been done linking smoking to oral fibrosis. However, it is well-established principally in studies from Southeast Asia, that smoking combined with betel nut chewing is associated with oral fibrosis and cancer (Norton, 1998).

Connective tissue growth factor (CCN2/CTGF), a multifunctional factor with a molecular weight of 38–40 kDa belonging to the Cyr61, CTGF, and Nov (CCN) family (Brigstock *et al.*, 2003; Perbal, 2004). Depending on the cell type studied, CCN2/CTGF can promote extracellular matrix production, cell migration and adhesion and proliferation either on its own or in concert with other factors (Leask and Abraham, 2006). CCN2/CTGF expression is associated with fibrosis (Leask *et al.*, 2009). In vivo evidence has recently been generated that suggest that overexpression of CCN2 can exacerbate fibrosis (Brigstock, 2010; Sonnylal *et al.*, 2009). Recently it was shown that an anti-CCN2 antibody could reduce some aspects of bleomycin-induced lung fibrosis (Ponticos *et al.*, 2009). However, relationships between smoking-associated fibrosis and CCN2/CTGF have not been shown.

A recent in vitro study used fibroblasts isolated from human gingivae and periodontal ligaments (PDL) and showed that nicotine could, albeit modestly, elevate production of type I collagen (Takeuchi *et al.*, 2010). In a manner that did not involve the induction of mRNA, addition of nicotine to oral fibroblasts resulted in increased CCN2 protein secretion by fibroblasts. Although unfortunately an appropriate control antibody was not used for the study, a neutralizing CCN2 antibody was able to reduce the ability of nicotine to induce type I collagen production by fibroblasts.

Although additional studies are required, for example with appropriate control antibodies in vivo and extensive in vivo work, these results suggest that the induction of CCN2/CTGF by nicotine may be a major promoter of periodontal fibrosis caused by smoking.

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