When there's smoke there's.....CCN2

Andrew Leask

Received: 30 July 2010 / Accepted: 5 August 2010 / Published online: 17 August 2010
© The International CCN Society 2010

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.

Keywords CTGF · Nicotine · Smoking · Betel nuts · Oral fibrosis · Gingiva

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. 2010). 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.

References

- Brigstock DR (2010) Connective tissue growth factor (CCN2, CTGF) and organ fibrosis: lessons from transgenic animals. J Cell Commun Signal 4:1–4
- Brigstock DR, Goldschmeding R, Katsube KI, Lam SC, Lau LF, Lyons K et al (2003) Proposal for a unified CCN nomenclature. Mol Pathol 56:127–128

A. Leask (✉)
Department of Dentistry, University of Western Ontario,
London, ON, Canada N6A 5C1
e-mail: Andrew.leask@schulich.uwo.ca

- Calsina G, Ramón JM, Echeverría JJ (2002) Effects of smoking on periodontal tissues. *J Clin Periodontol* 29:771–776
- Leask A, Abraham DJ (2006) All in the CCN family: essential matricellular signaling modulators emerge from the bunker. *J Cell Sci* 119:4803–4810
- Leask A, Parapuram SK, Shi-Wen X, Abraham DJ (2009) Connective tissue growth factor (CTGF, CCN2) gene regulation: a potent clinical bio-marker of fibroproliferative disease? *J Cell Commun Signal* 3:89–94
- Norton SA (1998) Betel: consumption and consequences. *J Am Acad Dermatol* 38:81–88
- Perbal B (2004) CCN proteins: multifunctional signalling regulators. *Lancet* 363:62–64
- Ponticos M, Holmes AM, Shi-wen X, Leoni P, Khan K, Rajkumar VS, Hoyles RK, Bou-Gharios G, Black CM, Denton CP, Abraham DJ, Leask A, Lindahl GE (2009) Pivotal role of connective tissue growth factor in lung fibrosis: MAPK-dependent transcriptional activation of type I collagen. *Arthritis Rheum* 60:2142–2155
- Sonnylal S, Shi-Wen X, Leoni P, Naff K, Van Pelt CS, Nakamura H, Leask A, Abraham D, Bou-Gharios G, de Crombrughe B (2010) Selective expression of connective tissue growth factor in fibroblasts in vivo promotes systemic tissue fibrosis. *Arthritis Rheum* 62:1523–1532
- Takeuchi H, Kubota S, Murakashi E, Zhou Y, Endo K, Ng PS, Takigawa M, Numabe Y (2010) Nicotine-induced CCN2: from smoking to periodontal fibrosis. *J Dent Res* 89:34–39