Novel Insights into Inflammatory Disturbed Bone Remodelling

Elin Kindstedt

Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av odontologie doktorsexamen framläggs till offentligt försvar i sal D, byggnad 1 D, 9tr, Tandläkarhögskolan, Norrlands Universitetssjukhus
Fredagen den 13:e oktober, kl. 09:00.
Avhandlingen kommer att försvaras på svenska.

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Abstract

Bone is a dynamic tissue that is continuously remodelled, a process that requires equal amounts of osteoclastic bone resorption and osteoblastic bone formation. Inflammation may disturb the equilibrium and result in local and/or systemic bone loss. Negative bone mass balance occurs in several chronic inflammatory diseases, e.g. periodontitis and rheumatoid arthritis (RA). The aetiology of periodontitis is infectious, while RA is an autoimmune disease. Despite aetiological differences, an association between the two diseases has been established but it is not known if they are causally related. Periodontitis may develop when the inflammatory process, initially restricted to the gingiva (gingivitis), further invades the periodontium and causes bone resorption. The cellular and molecular mechanisms underlying the transition from gingivitis to periodontitis are not fully elucidated. Osteoclast formation is dependent on receptor activator of nuclear factor kappa B ligand (RANKL), but how osteoclast precursors are recruited to the jawbone is poorly understood. A family of cytokines named chemokines has been reported to possess such properties and increasing evidence points towards their involvement in the pathogenesis of chronic inflammatory diseases.

The overall aim of this thesis was to gain extended knowledge about the role of chemokines and a newly discovered family of leukocytes named innate lymphoid cells (ILCs) in periodontitis and concomitant inflammatory disturbed bone remodelling. Furthermore, the aim was also to study the association between periodontitis and RA.

We identified increased serum levels of monocyte chemoattractant protein (MCP)-1 and CCL11 in individuals with periodontitis. Moreover, a robust correlation between the two chemokines and periodontitis was detected in a weighted analysis of inflammatory markers, subject characteristics and periodontitis parameters. We detected higher MCP-1 levels in periodontitis tissue compared to non-inflamed. Furthermore we demonstrated that human gingival fibroblasts express MCP-1 and CCL11 in response to pro-inflammatory cytokines through NF-κB signalling. Using an inflammatory bone lesion model and primary cell cultures, we discovered that osteoblasts express CCL11 in vivo and in vitro and that the expression increased under inflammatory conditions. Osteoclasts did not express CCL11, but its high affinity receptor CCR3 was upregulated during osteoclast differentiation and found to co-localise with CCL11 on the surface of osteoclasts. Exogenous CCL11 was internalised in osteoclasts, stimulated the migration of osteoclast precursors and increased bone resorption in vitro.

To analyse if periodontitis precedes RA we analysed marginal jawbone loss in dental radiographs taken in pre-symptomatic RA cases and matched controls. The prevalence of jawbone loss was higher among cases, and the amount of jawbone loss correlated with plasma levels of RANKL.

In the search of the newly discovered ILCs, we performed flow cytometry analyses on gingivitis and periodontitis tissue samples. We detected twice as many ILCs in periodontitis as in gingivitis. In addition we found RANKL expression on ILCs (an ILC subset).

In conclusion, we demonstrated that CCL11 is systemically and locally increased in periodontitis and that the CCL11/CCR3 axis may be activated in inflammatory disturbed bone remodelling. We also found that marginal jawbone loss correlated with plasma levels of RANKL and preceded clinical onset of symptoms of RA. Furthermore, we demonstrated that ILCs are present in periodontitis and represent a previously unknown source of RANKL.

Keywords

Bone resorption, inflammation, periodontitis, rheumatoid arthritis, chemokines, CCL11