Raising awareness of periodontal disease

Could you introduce the Clinical Research Unit 208 (CRU) at the University of Bonn and the current work you are carrying out?

The CRU 208 is an interdisciplinary research group which is funded by the German Research Foundation (DFG) and the Medical Faculty of the University of Bonn. The main goal is to improve the prevention, disease control and therapy of periodontitis through a better understanding of the causes and effects of periodontal diseases and the regenerative processes in the involved tissues.

The clinicians and scientists of the CRU 208 come from a range of departments at the University of Bonn, including Periodontology, Operative and Preventive Dentistry, Orthodontics, Oral Technology, Dermatology and Allergy, Internal Medicine, Cardiology, Pneumology and Angiology. There are also scientists from the University Hospital Schleswig-Holstein and the Institute of Computational Science at the University of Lugano.

There are several projects underway simultaneously at CRU. How do the projects communicate and collaborate with each other?

An interdisciplinary research approach has begun that comprises genetic, cell biological and biomechanical aspects. One project, with the assistance of other investigators of the CRU 208, has studied candidate genes involved in periodontitis. A number of projects have together examined whether cells derived from the tooth-supporting tissues participate in immune responses to oral bacteria. The projects also assisted each other in the isolation and cultivation of primary cells, microbial cultivation, the performance of different laboratory assays, the establishment of animal models and patient recruitment for clinical studies.

Why has the prevalence of these diseases increased dramatically over the past decades? How can your work help raise awareness of periodontal diseases?

Due to great success in the prevention and treatment of dental cavities over the past decades, people still have the majority of their teeth. In turn, more teeth are at risk of experiencing periodontitis. The CRU 208 has made significant efforts to share its findings with the dental community and the general public. Several reports have been published by the CRU 208 in dental and non-dental journals and interviews have been given on radio and television. Furthermore, a website has been established in order to make information on the CRU 208 and its projects available to the public.

Have you made any progress on your aim to investigate the mechanisms for the association of periodontitis with systemic diseases?

One project identified ANRIL as a shared genetic risk factor for periodontitis and coronary heart disease. This project could replicate the association in several European populations of periodontitis and showed the regulation of ANRIL by pathogenic bacterial infection. These findings indicate that coronary heart disease and periodontitis are in part genetically related. In a pre-clinical study, it was observed that adiponectin may counteract critical actions of periodontopathogenic bacteria on oral epithelial cells. Low levels of adiponectin, as observed in obese individuals, may increase the risk for periodontal inflammation and destruction.

How do you excite and involve the younger generation of researchers to pursue this field of research?

The CRU 208 was greatly concerned with involving the younger generation of researchers as well as students with a special interest in periodontal diseases and biomechanics into the projects. Although the promotion of junior scientists also took place in every project, one project was entirely dedicated to this purpose. PhD positions were filled with non-dental candidates in order to strengthen the connection between dentistry and natural sciences. At our international symposium, junior scientists had the opportunity to present their findings to the wider research community.
Understanding periodontitis

At present, knowledge about the development and progression of periodontitis is still incomplete. Researchers at the University of Bonn are studying the pathophysiology behind this increasingly prevalent disease.

PERIODONTITIS IS A COMPLEX multifactorial inflammatory disease which is characterised by the destruction of tooth-supporting tissues. The disease has an enormously negative impact on a wide range of psychological, physical and social aspects of quality of life in affected individuals and thus also poses a significant economic problem. In addition, there is increasing evidence that periodontitis is associated with a range of systemic diseases and conditions including diabetes, cardiovascular diseases, obesity, preterm low birth weight and arthritis. An estimated 70 per cent of the German population aged between 35 and 44 suffers from periodontitis, with evidence that prevalence of the disease is increasing.

An inflammatory process caused by bacterial components and products triggers the production of inflammatory molecules by infiltrating resident cells in the periodontium. These inflammatory mediators can result in progressive destruction of the periodontal tissues and, thereby, in pocket formation and tooth loss. However, the exact aetiopathogenetic mechanisms for periodontitis are still largely unknown, meaning that therapy is restricted to unspecific interventions such as improvement of oral hygiene, mechanical removal of subgingival biofilm, topical application of antimicrobial substances, or systemic administration of antibiotics. Hence, elucidating the underlying mechanisms leading to the initiation and chronic manifestation of periodontitis could give rise to new and more specific therapeutic strategies.

EXPLORING PROCESSES

The Clinical Research Unit (CRU) 208 funded by the German Research Foundation (DFG) and the Medical Faculty of the University of Bonn, Germany, is exploring the inflammatory, tissue-destructive and regenerative processes in the periodontium and possible sequelae for general health in the context of *in vitro* animal and clinical studies.

Professor James Deschner, Head of CRU 208, as well as Professors Søren Jepsen and Andreas Jäger (both speakers of the CRU 208), explain the Unit’s achievements so far: “Our projects have examined the immunoinflammatory processes in periodontal tissues; the regulation of the inflammatory and tissue-destructive processes by various intrinsic and extrinsic factors; the mechanisms by which local periodontal inflammation and destructive processes cause systematic vascular damage; and finally, how the regeneration of lost periodontal structures is initiated or supported by growth and differentiation factors”.

COUNTERACTING PRO-INFLAMMATORY MECHANISMS

One of the Unit’s projects has demonstrated that antimicrobial peptides (AMPs), such as human beta-defensins (hBDs), are upregulated in gingival cells in response to oral commensal and periodontopathogenic bacteria. These findings demonstrate that cell–bacteria interactions and/or bacteria-bacteria cross-talk may impact on the regulation of AMPs in the gingival tissue. A better understanding of the regulation of AMPs during host–bacteria-interactions is a pre-requisite for future novel antimicrobial treatment strategies, using AMPs as exogenous therapeutic agents or by stimulation of the endogenous peptide expression.

As a result of a project that is investigating the genetic background of periodontitis, variants in the hBD-1 and cyclooxygenase II genes, which are involved in the innate immune-inflammatory response, were found to be associated with periodontitis. In another project it was shown that interleukin (IL)-17 producing $T_b$ cells predominate at severe inflammatory sites of chronic periodontitis. The amount of $T_h$ cells in the lesion was directly related to the number of IL-23p19 producing macrophage-like/dendritic cells (Mo-like cells). Additionally, lipopolysaccharide from the periodontopathogenic microorganism *P. gingivalis* was able to induce IL-23p19 production in Mo-like cells in response to TLR4 activation and might thereby propagate the Th17 predominated infiltrate in chronic periodontitis. IL-23p19 and IL-17 blockage may, therefore, represent a novel therapeutic approach to counteract pro-inflammatory mechanisms in chronic periodontitis.

REGULATION OF REGENERATIVE PROCESS

Further research at CRU 208 examined whether the regenerative capacity of periodontal ligament (PDL) cells in the presence of enamel matrix derivative (EMD) is modulated by inflammation and/or biomechanical forces. EMD stimulated the wound fill rate, cell proliferation, adhesion and differentiation, synthesis of growth factors and matrix molecules, as well as mineralisation. However, in the presence of inflammatory and/or biomechanical signals, these EMD effects were significantly reduced. These findings demonstrated that the beneficial actions of EMD on PDL cell functions critical for periodontal regeneration are jeopardised by inflammatory and/or biomechanical signals. Furthermore, a separate investigation by CRU 208 members revealed that insulin-like growth factor 1 and 2 are critical to...
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Periodontal homeostasis and that their activities are modulated by inflammation, biomechanical forces and hypoxia. Another project provided data on PDL cells and their response to intermittent parathyroid hormone (PTH) treatment. The assumption was substantiated that these cells contribute significantly to the regulation of periodontal tissue remodelling and may be directed in this process by PTH.

PERIODONTITIS AND VASCULAR DAMAGE

Recent clinical and epidemiological investigations have demonstrated that severe periodontitis causes endothelial dysfunction and may be associated with coronary artery disease and an increased cardiovascular event rate. The molecular and cellular mechanisms are incompletely understood at present.

Ongoing work aims to elucidate the impact of periodontitis on vascular damage and repair and the role of vascular regeneration in the treatment of periodontitis. The researchers have found a seemingly defective progenitor mobilisation from the bone marrow into peripheral blood in experimental periodontitis in atherosclerosis-prone mice, which could provide a novel mechanistic link of increased atherogenesis and periodontal infections. This will help to establish new strategies for the treatment of periodontal disease that may improve local treatment success and also decrease cardiovascular risk.

IMPROVING THERAPEUTIC INTERVENTIONS

With its next round of funding, the major goal of the CRU 208 remains to improve the prevention, disease control and therapy of periodontal diseases through a better understanding of the aetiopathogenetic and regenerative processes. "Our projects will continue to identify immunological mechanisms critical not only for the initiation, but also for the chronic manifestation of periodontitis," Deschner enthuses. "They will serve to obtain a rational basis for specific therapeutic interventions."

The CRU 208 will further explore the innate and adaptive immune responses to bacterial infections. The researchers will study the role of macrophages/dendritic cells and natural killer T cell interactions in the pathophysiology of chronic periodontitis. They will also analyse the antimicrobial response of gingival cells to oral bacteria and study the role of antimicrobial peptides in gingival inflammation, periodontal healing and oral neoplasia.

These projects will help further identify immunological mechanisms critical for the initiation and chronic manifestation of periodontitis. Additional factors such as systemic diseases contribute to the development of periodontitis, and oxidative stress may act as a potential common link between periodontitis and systemic diseases, including cardiovascular diseases, diabetes mellitus and obesity, the prevalence of which has increased dramatically over the past decades. The CRU 208 is therefore focusing on the underlying mechanisms for the association of periodontitis with systemic diseases. "These projects aim at contributing to a better understanding of the interactions of systemic diseases and factors with periodontal homeostasis, destruction and regeneration," Jepsen and Jäger explain. "They may also guide the development of prognostic and diagnostic markers and could pave the way for future therapeutic applications."

The CRU 208 has a further focus on the role of vascular regeneration in the treatment of periodontitis on vascular damage and repair and the role of vascular homeostasis and that their activities are modulated by inflammation, biomechanical forces and hypoxia. Another project provided data on PDL cells and their response to intermittent parathyroid hormone (PTH) treatment. The assumption was substantiated that these cells contribute significantly to the regulation of periodontal tissue remodelling and may be directed in this process by PTH.

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