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Rational development of nanomedicines for molecular targeting in periodontal disease

Nikola Geskovski[a], Simona Dimchevska Sazdovska[a], Silvana Gjosheva[a], Rumenka Petkovska[b], Mirjana Popovska[c], Liljana Anastasova[b], Kristina Mladenovska[a], Katerina Goracinova[a,d,*]

[a] Institute of Pharmaceutical Technology, Faculty of Pharmacy, University of Ss Cyril and Methodius, Skopje, Macedonia
[b] Institute of Applied chemistry and Pharmaceutical Analysis, Faculty of Pharmacy, University of Ss Cyril and Methodius, Skopje, Macedonia
[c] Department of Oral Pathology and Periodontology, Faculty of Dentistry, University of Ss Cyril and Methodius, Skopje, Macedonia
[d] College of Pharmacy, Qatar University, PO Box 2713, Doha, Qatar

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ABSTRACT

Recent advances in understanding the etiology and pathogenesis of periodontal disease and polymicrobial synergy in the dysbiotic oral microbial community endorsed novel therapeutic targets and assured further improvement in periodontal disease treatment. Moreover, understanding of the events at the molecular level inspired the researchers to alleviate the stress from the disease by applying the bottom-up approach and delivering the drugs at the site of action, using nanoscale medicines. This review is focused on promising strategies for rational design of nanopaharmaceuticals for periodontal disease treatment based on novel therapeutic targets and the potential of advanced concepts for inflammation cascade targeting. Due to their size, nanomedicines are capable to interact with the elements of the immune system through cell receptor binding and to subsequently influence specific intracellular signaling pathways activation. They might also interfere with different signaling molecules continuously involved in the disease progression, in order to abolish cell activation and block the production of proinflammatory substances. Different biomacromolecules can be trafficked to the site of action using nanomedicines for gene targeting: i) decoy oligodeoxynucleotide (ODN) for suppression of NF-κB transcription activity, ii) DNA therapeutics for modulation of cell inflammatory response and iii) siRNA for cytokine production silencing. However, despite the potential of the nanotechnology for improvement of periodontal disease treatment, the translation of nano-drug delivery systems to clinical therapy is hindered by the lack of standard procedures for proper safety and efficacy profile evaluation.

1. Introduction

Periodontal disease is a complex problem with fairly unpredictable therapeutic results, often interrelated with adverse medical outcomes of several serious systemic diseases. Worldwide there is a large prevalence of periodontitis in a range between 13-54% in different countries and people of different ages are affected with this condition (Álvarez, Espinar, & Méndez, 2011; Greenberg & Glick, 2003; Hugoson & Norderyd, 2008).

The major breakthrough in the periodontal disease research was in the early 1980's when it was acknowledged that although bacteria are the primary etiological cause of this illness, the expression of bacterial pathogenic factors alone is probably not sufficient to cause periodontitis and that the basement of the pathology is of inflammatory nature (Howell & Williams, 1993; Reddy et al., 2011). Nowadays, it is known that the innate immune response generated at the periphery of sites of microbiological penetration, as a silent and physiological inflammatory response, is essentially protective in design (Sansonetti & Di Santo, 2007). However, the excessive host response, as well as the amplification of the initial inflammatory reaction (lasting approximately 21 days), might result in inadequate resolution of the inflammation which is critical to the pathogenesis of periodontitis (Bascones-Martínez et al., 2009; Di Benedetto, Gigante, Colucci, & Grano, 2013; Gierut, Perlman, & Pope, 2010). Failure of protective aspects of the host response, dysfunctional regulatory mechanisms and hyper-responsive host defense reaction in certain individuals will cause homeostatic mechanisms disruption and will result in continuous release of proinflammatory mediators (IL-1, IL-6, TNF-a, prostaglandin E2). This will lead to chronic inflammation, progression of gingival inflammation to periodontal disease, extracellular matrix destruction in the gingiva and bone resorption (Baker, 2000; Darveau, 2010; Dyke & Winkelhoff, 2013; Graves, Li, & Cochran, 2011; Noh et al., 2013). Undoubtedly, the

* Corresponding author at: Institute of Pharmaceutical technology, Faculty of Pharmacy, University Ss Cyril and Methodius, Mother Teresa 47, 1000 Skopje, Macedonia.
E-mail address: kago@ff.ukim.edu.mk (K. Goracinova).

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severity of the host response to periodontitis inducing factors is usually strongly determined by the genetic and immunologic profile of the patient, modified by environmental risk factors and systemic disease disorders (Kornman, 2008; Yucel-Lindberg & Båge, 2013). These facts strongly point to a two-way relationship between periodontal disease and the systemic health of an individual (Dumitrescu & Kawamura, 2010; Friedewald et al., 2009; Persson & Persson, 2008; Pucher & Stewart, 2004; Salvi et al., 2008).

Recent therapeutic advances are based on the understanding of the cytokine signaling pathways that favor chronic inflammation in periodontitis. Novel improved therapeutic approaches for host cell signaling pathways modulation and the recovery of the balance of proinflammatory and anti-inflammatory mediators, have found their way as promising treatments in periodontal disease (Kirkwood, Cirelli, Rogers, & Giannobile, 2007; Souza, Junior, Garlet, Nogueira, & Cirelli, 2012; Van Dyke & Serhan, 2003). However, the potential side effects of the host defense system modulation including hemorrhage, gastrointestinal problems as well as renal and hepatic impairment might restrict the use of these novel substances, especially their systemic administration (Deshmukh, Jawali, & Kulkarni, 2011). A further drawback is their instability in a biological environment and limited potential to readily cross the biological membranes in order to reach the site of action (Adessi & Soto, 2002). Therefore, novel approaches in the clinical treatment of periodontal disease require development of strategies for efficient drug delivery at the site of inflammation. In order to accomplish this task, employment of novel micro and nanoparticulated drug delivery systems as carriers for newly developed drug substances is essential.

Having in mind what was previously mentioned, this review will be focused on the newly discovered targets and novel active substances in the clinical treatment of periodontal disease as well as sophisticated therapeutic systems for efficient delivery of these drugs at the site of action.

1.1. Etiology and pathogenesis of periodontitis – host cell response pathways and polymicrobial synergy

1.1.1. Biofilm and quorum sensing

Nowadays, it is beyond any doubt that we are hosts for several hundred bacterial species (800-1000 different bacterial species with varying abundance and diversity patterns across age and health status have been identified) that form the community of dental plague in our oral cavity (Dewhirst et al., 2010; Gomez & Nelson, 2017; Paster et al., 2001). Moreover, there is a wide agreement on the etiological role of the oral microbiome in human periodontal disease. Therefore, during the pursuit of its etiological agents vast amount of research is dedicated to the development of different models of the dynamics of this unique ecosystem, its association with periodontal disease pathology, assessment of its composition, morphology, oral biofilm formation, dental calculus localization and anticalculus agents (Gomez et al., 2017; Haffajee & Socransky, 1994; Saglie, Carranza, Newman, Cheng, & Lewin, 1982; Socransky & Haffajee, 1992; Socransky, 1970). As the research evolved, the criteria for defining the pathogens in periodontal disease evolved as well. The conventional view that early disease development can be associated with the so-called “orange complex” bacteria (consisting of Gram-negative, anaerobic species such as *Prevotella intermedia* and *Fusobacterium nucleatum*), and shifts to the so-called “red complex” species as the disease worsens (consisting of periodontal pathogens *Porphyromonas gingivalis*, *Tannerella forsythia*, and *Treponema denticola*), probably needs a refinement, particularly on the issue - how the microbial communities manage the disease progression (Bodet, Chandad, & Grenier, 2006; Hajishengallis & Lamont, 2012; Holt & Ebersole, 2005; Mineoka et al., 2008).

Further, the fact that periodontal bacteria are usually present in combination in periodontal pockets rather than alone, suggests that they actually cause a destruction of the periodontal tissue in a cooperative manner (Yoneda et al., 2005). During the process of biofilm development, from an early stages when it is comprised of a single microbial cell layer attached to a surface trying to build their quorum, the microbiota signal each other how to reorganize and form a dense structure numerous layers thick. These formations with an array of pillars and irregular surfaces, are all connected by convoluted channels that deliver food and remove waste (Strużycka, 2014). The microbiota communication system termed “quorum sensing” facilitates sending out chemical signals that trigger the bacteria to increase their pathogenicity, produce potentially harmful proteins, enzymes or virulence factors that will help the intraoral biofilm to evade or bypass host defense systems or deregulate the immuno-inflammatory response (Dumitrescu & Kawamura, 2010). Additionally, when compared to the planktonic or free cell state, the biofilm produces extracellular matrix, which shields the bacteria from the environment and contributes to their improved resistance to antibiotics in this ecosystem (Kerksiek, 2008). It is apparent that the interactions among different microbial species at several levels, including physical contact, metabolic exchange, and signal-mediated communications will determine characteristics and virulence of the biofilm. More precisely, although the red complex bacteria have been shown to be most associated with the late stage of subgingival plaque development, further shift to periodontitis depends on the biofilm virulent microbiota community as well as their potential to deregulate the host immuno-inflammatory reaction and collectively cause chronic disease (Bodet, Chandad, & Grenier, 2007; Holt & Ebersole, 2005; Socransky, Haffajee, Cugini, Smith, & Kent, 1998). Accordingly, understanding of the interaction between typical pathogenic bacteria or well adopted opportunistic pathogens like *Porphyromonas gingivalis* and the host is essential for prevention, prognosis, and treatment of this disease as well as for the development of novel strategies for its eradication (Petersen & Ogawa, 2005). Numerous findings confirm the strong potential of biofilm periodontopathogens for activating host-mediated destructive processes and their indisputable connections with the host inflammation mechanisms (Zhao, La, & Grenier, 2013). Obviously, complex microbial community impacts the host cells response within the gingival crevice in a different manner distinct from the sum of activities of its constituents. The outcome of the bacterium-epithelial cell interaction, when the host cells recognize the infecting bacteria and tailor a response while the bacteria attempt to manipulate host cell responses, is crucial for establishing pathogenic potential (Han et al., 2000). During these events, the initiation and maturation of the immuno-inflammatory response to the intraoral bacteria will influence the disease outcome. It is likely that dysregulated host response will increase the probability of collateral tissue damage and disease progression to periodontitis (Bartold & Van Dyke, 2013; Zhao et al., 2013).

1.1.2. Innate, adoptive host immunity response and host susceptibility factors

Host susceptibility factors may be traced back to the level of the mutual interaction between resident microbiological supra and subgingival plaque species and more important between virulent bacteria and the host tissue. This interaction is triggered through the elements of the innate and adaptive immune response (Fig. 1) (Ishii, Koyama, Nakagawa, Coban, & Akira, 2008). Multiple host cells of myeloid and non-myeloid origin including oral keratinocytes, neutrophil polymorphs, macrophages, monocytes, dendritic cells, osteoblasts and osteoclasts are involved in the disease development and resolution. At the same time, the epithelial cells and the neutrophils in the periodontal connective tissue are the first to interact with the plaque bacteria and their products through cell receptor binding and specific intracellular signaling pathways activation (Dennison & Dyke, 1997; Page, Offenbacher, Schroeder, Seymour, & Kornman, 1997; Sahingur & Yeudall, 2015).

If the inflammatory cells and processes are able to contain bacterial challenge and their products after an initial innate immune response, the disease will limit itself to the gingiva and predominant T cell/