synchronizing interaction between the innate and adaptive immune systems by tightly regulating their activities. The innate immune system is regarded as the first line of defense against bacterial pathogens, including periodontopathogens [16]. VDR inhibits the differentiation, maturation and immune stimulating ability of dendritic cells by down-regulating the expression of Major Histocompatability Complex class II molecules [17]. This inhibition maintains dendritic cells in an immature state that present phenotypes that promote T-cell tolerance [17]. At the same time, VDR suppresses interleukin (IL)-12 production and enhances IL-10 production in dendritic cells [17]. VDR regulates the production of T-cell helper 1 and 2 cytokines and IL-17, by which it influences adaptive immunity and inflammation [18]. Furthermore specific T-cell cytokines are able to influence the TLR-induced VDR-dependent antimicrobial pathway in human monocytes. The TH1 cytokine interferon γ enhances the TLR2/1 induction of CYP27B1, cathelicidin [18]. Cathelicidins have significant broad antimicrobial activity against both gram-positive and gram-negative bacteria [17].

Th1/Th2/Th17 paradigm: For decades the Th1/Th2 paradigm was utilized to explain chronic inflammation associated with periodontal disease [19]. Comprehensive descriptions regarding the role of Th1 and Th2 cytokines in periodontal inflammation are available elsewhere and will thus not be reviewed in this manuscript [20,21]. More recently, another subset of the Th cells, identified as Th17 has been added to this paradigm and has helped in elucidating some of the weaknesses in the original Th1/Th2 theory [19,22]. Th17 cells have been detected in periodontal epithelia and these cells secrete IL-17 which, in turn, induces the production of IL-6, IL-8 and prostaglandin, as well as the activation of nuclear factor kappa B ligand (RANKL) in osteoblasts, thereby inducing osteoclastic bone resorption [19,23]. Following binding to its receptor, RANK, RANKL steers the differentiation to a mature osteoclast that displays resorptive capacity in bone [19]. To counteract this, Osteoprotegerin (OPG) receptor acts as a "decoy receptor" that is able to directly bind to RANKL, thereby inhibiting osteoclast maturation trough inhibition of RANKL/RANK complex [19]. As a result, OPG acts as shielding cytokine that prevents bone resorption [19]. Worthy of note is the finding that IL-17 favours bone loss through modulation of RANKL/OPG ratio in favour of RANKL expression in osteoblasts [24]. To sum up, Th17 in unison with Th1 cells participate in destruction of tissue and bone in periodontal disease.

VDR thus plays a crucial immunomodulatory role by inhibiting antigen induced T-cell proliferation such as Th1 and Th17 as well as cytokine production [10].

Periodontal disease and immune subversion strategies of periodontopathogens: Periodontal disease is a chronic inflammatory disease that causes tissue damage and steadily leads to alveolar bone loss and ultimately, tooth loss [25]. This gradual destruction of bone is owed to the periodontopathogens that produce an immune response [26]. Traditional management of chronic periodontal disease was directed towards the mechanical removal of the bacterial agents; however this approach did not provide considerable clinical improvements [26]. More recently, management of chronic periodontal disease has been focused on augmented vitamin D supplementation owing to the fact that $1,25(OH)_2D_3$ has been recognized as an essential immunomodulatory agent [17]. Clinical observations that $25(OH)D_3$ levels were reduced in periodontal disease and the assumption that low levels of $25(OH)D_3$ must be the cause of periodontal disease prompted its clinical administration [17,27]. In fact, the general administration of $25(OH)D_3$ in infectious disease may disturb the immune response by hindering the functions of vitamin D nuclear receptor (VDR) [28,29]. Elevated $1,25(OH)_2D_3$ have also been shown to bind to pregnane X nuclear receptor thereby impeding the capacity of CYP24A1 to control the levels of $1,25(OH)_2D_3$ [28,29]. Consequently conversion of $25(OH)D_3$ in the liver is inhibited which leads to the clinical expression of low levels of $25(OH)D_3$ encountered in inflammatory diseases [28,29].

In order to achieve the desired long-term therapeutic effects, development of immunomodulatory treatment strategies are required. Periodontal epithelium provides the primary barrier to infection and has an active role in the innate host defences against periodontopathogens [30]. The "red-complex" group of periodontal pathogens exhibits the strongest correlation to periodontitis [31]. This group comprises of *Porphyromonas gingivalis, Tannerella forsythia* and *Treponema denticola.* The front-runner of this group is considered to be *Porphyromonas gingivalis* that is assumed to be a "keystone species" as it "serves an essential function for the entire community, similar to a differentiated cell serving a function for an entire tissue" [32]. *P. gingivalis* is an obligate anaerobe, biofilm producing bacterium that presents several virulence factors, amongst others, atypical lipopolysaccharides (LPS), fimbria and cysteine proteinases also known as, gingipains [33]. *P. gingivalis* is typically known for its ability to form a subgingival bacterial biofilm within the periodontal pocket [34]. *P. gingivalis* is able to persist within macrophages by evolved strategies that subvert the host's immunity and secures a niche by manipulating key features of innate immunity, particularly Toll-like receptors and the complement system which have direct roles in adaptive immunity [34-36]. It has been demonstrated that *P. gingivalis* has the capacity to cross epithelial barriers and has been detected in remote sites in the human body [37]. It is thus strongly implicated in distant systemic inflammatory responses in several chronic diseases, such as atherosclerosis [38]. *P. gingivalis* express unfamiliar LPS molecules that can directly antagonize TLR4 [39]. This in turn impedes the expression of antimicrobial peptides such as β-defensins in the host's epithelial cells [39]. *P. gingivalis* also has the capacity to hinder TLR4-mediated immune response against other similar bacteria thereby facilitating a niche for other pariodontopathogens [39].

P. gingivalis is recognized by the innate immune system mainly through TLR2, but *P.gingivalis* is unable to antagonize TLR2 directly [32]. Interestingly, *P. gingivalis* has developed undermining interactions between TLR2 and other receptors of the innate immune system which allows it to indirectly diminish the TLR2 antimicrobial response [32]. Through complex inside-out signalling of TLR2, *P. gingivalis* binds to transactivated CR3 of the compliment system through its fimbria, thereby stimulating phagocytosis by macrophages [40]. CR3 mediated phagocytosis is not associated with a robust antimicrobial mechanism and thus does not stimulate lysing of *P.gingivalis* once inside the macrophage and, as a result it is able to chronically persist within these immune cells [41].

***P. gingivalis* and Th1/Th17 response:** CD4+ T-cells mediate immunity against pathogens by modulating the Th1 or Th2 type response [19]. *P.gingivalis* appears to primarily induce a Th-1 cell type response [14]. In addition to the Th-1 cell type response, it has been shown that the protein located on the membrane of *P. gingivalis* also has the ability to significantly increase the secretion of IL-17, which represents the principal cytokine secreted by TH17 cells within the periodontium [19,33] *P. gingivalis* is able to induce Th-17 differentiation by various mechanisms [33]. One such mechanism is the expression a specific virulence factors which, through TLR2 ligands signalling, activate NFkB-dependent proinflammatory pathways in monocytes and dendritic cells [33]. *P. gingivalis* also influences the release of Th17 cytokines, namely IL-1β, IL-6 and IL-23 [33]. Th-17 development is driven predominantly by monocytes and dendritic cells [33].

Thus insufficient clearance of intracellular bacteria coupled with a deregulated release of pro-inflammatory cytokines in considered as a trigger of periodontal disease [42].

VDR and *P. gingivalis*

It has been demonstrated that VDR plays an important role in both the innate and the adaptive immune response to *P.gingivalis* [14]. Of significance is the fact that VDR deficient mice are increasingly more susceptible to infection with *P gingivalis* and are unable to mediate intracellular lysis of bacteria and hence show an increased bacterial burden [14]. Both VDR gene polymorphism and Vitamin D resistant rickets has been linked to a greater susceptibility to aggressive periodontitis and VDR gene risk marker is being used as a vulnerability test to periodontal disease [14]. VDR has also been shown to inhibit IL-8 expression induced by *P.gingivalis* in periodontal ligament cells and thus has anti-inflammatory effects in periodontal disease [43].

VDR agonists

It is currently recognized that VDR has a modulatory effect on the immune response against *P.gingivalis* through its anti-inflammatory role and the fact that it aids in intracellular clearance of the bacteria. The biological activity of Vitamin D is thus dependent both on the adequate production and distribution of 1, 25 $(OH)_2D_3$ as well as adequate expression of VDR [1]. In individuals with functioning VDR, $1,25(OH)_2D_3$ has been considered a therapeutic agent for the treatment of periodontal inflammation[43]. But the high levels of $1,25(OH)_2D_3$ that are needed in order to bring about an adequate immunomodulatory response, result in unwanted hypercalcemia due to up-regulation of calcium ion channel transient receptor potential vanilloid type 5 and 6 (TRPV 5-6) through VDRE [9,43]. Duodenal TRPV6 has been identified as an important mediator of $1,25(OH)_2D_3$, leading to calcium absorption from the intestine [9]. Investigations carried out on inflammatory and autoimmune diseases have elucidated a VDR agonist, elocalcitol, as a potent VDR agonist and potential therapy that is able to ameliorate abnormal inflammation without calcium increasing capacity [9,44]. Elocalcitol exerts an anti-inflammatory as well as a regulatory effect on both the innate immune response and the adaptive immune response [9]. Elocalcitol interferes with the differentiation of dendritic cells, thereby preventing their maturation and modulates Th17 cells by inhibiting the production of IL-17 [9]. Furthermore, elocalcitol down-regulates pro-inflammatory Th1 cells and has the potential to augment the development of Th2 cells thereby moderating tissue damage in chronic inflammation [9]. Such or similar agonists may be used in ameliorating the inflammatory response in periodontitis due to the fact that VDR has been directly implicated in immune response to *P.gingivalis* [14]. Moreover, inflammatory cytokines, amongst others, IL-17 provide a viable link between periodontal disease and systemic disease [19]. Periodontal disease is also considered a risk factor for an assortment of systemic diseases ranging from exacerbated cardiovascular disease, to rheumatoid arthritis [19,45]. Understanding the degree to which VDR agonists are capable of regulating inflammatory cytokines involved in both oral and systemic diseases whilst enhancing the intracellular lysing capacity of cells of the immune system would thus be of great therapeutic significance in periodontal disease as well as a wide-range of systemic disease.

Summary

Regulation of VDR is a shared defence mechanism against periodontopathogen *P.gingivalis* of both the innate and adaptive immune system. It regulates the functions of dendritic cells and stimulates the secretion of antimicrobial peptides at the site of infection and appears to largely inhibit pro-inflammatory pathogenic T- cells subsets and thus mediate inflammation and tissue damage.

Chronic inflammation of the periodontal tissues has been demonstrated to have significant negative effect on the overall health of individuals suffering from the disease. It is thus apparent that adjusting the activity of VDR clinically may play an important role in shaping the immunomodulatory effects of vitamin D as well as on the overall health of patients by decreasing the activity of cytokines such as IL-17 which are important links between oral and systemic disease.

Periodontitis is a chronic disease confounded by several factors, including environmental and genetic factors that play a part in disease pathogenesis. The current understanding of the link between VDR and *P.gingivalis* highlighted in this article could nevertheless facilitate the development of effective designs for augmenting VDR expression and activity through potent VDR agonists, fine-tuned for minimizing periodontal associated inflammation.

These observations provide a new research arena for VDR agonists with potent anti-inflammatory properties without adverse systemic effects to be used in the anti-inflammatory treatment of periodontal disease.

References

1. Kongsbak M, Levring TB, Geisler C, von Essen MR (2013) The vitamin d receptor and T cell function. Front Immunol 4: 148.
2. Kreutz M, Andreesen R, Krause SW, Szabo A, Ritz E, et al. (1993) 1,25-dihydroxyvitamin D3 production and vitamin D3 receptor expression are developmentally regulated during differentiation of human monocytes into macrophages. Blood 82: 1300-1307.
3. Hewison M, Freeman L, Hughes SV, Evans KN, Bland R, et al. (2003) Differential regulation of vitamin D receptor and its ligand in human monocyte-derived dendritic cells. J Immunol 170: 5382-5390.
4. Geldmeyer-Hilt K, Heine G, Hartmann B, Baumgrass R, Radbruch A, et al. (2011) 1,25-dihydroxyvitamin D3 impairs NF-ÎºB activation in human naÃ¯ve B cells. Biochem Biophys Res Commun 407: 699-702.
5. Joseph RW, Bayraktar UD, Kim TK, St John LS, Popat U, et al. (2012) Vitamin D receptor upregulation in alloreactive human T cells. Hum Immunol 73: 693-698.
6. McCollum EV (1957) A history of Nutrition. (1stedn), Houghton Mifflin Company, Boston, USA.
7. Farber E (1953) Nobel Prize Winners in Chemistry. (1stedn), Abelard-Schuman, New York, USA.
8. Wolf G (2004) The discovery of vitamin D: the contribution of Adolf Windaus. J Nutr 134: 1299-1302.
9. Mora JR, Iwata M, von Andrian UH (2008) Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol 8: 685-698.
10. Laverny G (2009) Identification of a potent and safe VDR agonist for the treatment of inflammatory bowel disease. [Thesis]. University of Kuopio, Kuopio Yliopisto, Finland. p135.
11. Bell NH (1998) Renal and nonrenal 25-hydroxyvitamin D-1alpha-hydroxylases and their clinical significance. J Bone Miner Res 13: 350-353.
12. Manchanda PK, Kibler AJ, Zhang M, Ravi J, Bid HK (2012) Vitamin D receptor as a therapeutic target for benign prostatic hyperplasia. Indian J Urol 28: 377-381.
13. Carlberg C (2003) Current understanding of the function of the nuclear vitamin D receptor in response to its natural and synthetic ligands. Recent Results Cancer Res 164: 29-42.
14. Yezdani G (2011) Role of VDR in host immune response to Porphyromonas gingivalis infection. [Thesis]. University of Alabama, Birmingham, Alabama, USA. p42.

15. Nagpal S, Na S, Rathnachalam R (2005) Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 26: 662-687.

16. Rasmussen SB, Reinert LS, Paludan SR (2009) Innate recognition of intracellular pathogens: detection and activation of the first line of defense. APMIS 117: 323-337.

17. Anand N, Chandrasekaran SC, Rajput NS (2013) Vitamin D and periodontal health: Current concepts. J Indian Soc Periodontol 17: 302-308.

18. Tiosano D, Wildbaum G, Gepstein V, Verbitsky O, Weisman Y, et al. (2013) The role of vitamin D receptor in innate and adaptive immunity: a study in hereditary vitamin D-resistant rickets patients. J Clin Endocrinol Metab 98: 1685-1693.

19. Suresh S (2011) A new paradigm in autoimmunity-role in periodontal disease. Ind J of Dent Adv 3:583-586.

20. Gemmell E, Seymour GJ (2004) Immunoregulatory control of Th1/Th2 cytokine profiles in periodontal disease. Periodontol 2000 35: 21-41.

21. Muraille E, Leo O (1998) Revisiting the Th1/Th2 paradigm. Scand J Immunol 47: 1-9.

22. Weaver CT, Murphy KM (2007) T-cell subsets: the more the merrier. Curr Biol 17: R61-63.

23. Fossiez F, Djossou O, Chomarat P, Flores-Romo L, Ait-Yahia S, et al. (1996) T cell interleukin-17 induces stromal cells to produce proinflammatory and hematopoietic cytokines. J Exp Med 183: 2593-2603.

24. Sato K, Suematsu A, Okamoto K, Yamaguchi A, Morishita Y, et al. (2006) Th17 functions as an osteoclastogenic helper T cell subset that links T cell activation and bone destruction. J Exp Med 203: 2673-2682.

25. Lane J (2013) Investigation into toll like receptor mechanisms of action, in relation to Porphyromonas gingivalis in periodontitis. The Plymouth Stud Scien 2: 355-367.

26. Di Benedetto A, Gigante I, Colucci S, Grano M (2013) Periodontal disease: linking the primary inflammation to bone loss. Clin Dev Immunol 2013: 503754.

27. Garcia MN, Hildebolt CF, Miley DD, Dixon DA, Couture RA, et al. (2011) One-year effects of vitamin D and calcium supplementation on chronic periodontitis. J Periodontol 82: 25-32.

28. Albert PJ, Proal AD, Marshall TG (2009) Vitamin D: the alternative hypothesis. Autoimmun Rev 8: 639-644.

29. Waterhouse JC, Perez TH, Albert PJ (2009) Reversing bacteria-induced vitamin D receptor dysfunction is key to autoimmune disease. Ann N Y Acad Sci 1173: 757-765.

30. Mariano FS, Sardi JO, Duque C, Höfling JF, Gonçalves RB (2010) The role of immune system in the development of periodontal disease: a brief review. Rev odonto scienc 25: 300-305.

31. Socransky SS, Haffajee AD, Cugini MA, Smith C, Kent RL Jr (1998) Microbial complexes in subgingival plaque. J Clin Periodontol 25: 134-144.

32. Hajishengallis G (2011) Immune evasion strategies of Porphyromonas gingivalis. J Oral Biosci 53: 233-240.

33. Moutsopoulos NM, Kling HM, Angelov N, Jin W, Palmer RJ, et al. (2012) Porphyromonas gingivalis promotes Th17 inducing pathways in chronic periodontitis. J Autoimmun 39: 294-303.

34. Kuboniwa M, Lamont RJ (2010) Subgingival biofilm formation. Periodontol 2000 52: 38-52.

35. Flannagan RS, Cosío G, Grinstein S (2009) Antimicrobial mechanisms of phagocytes and bacterial evasion strategies. Nat Rev Microbiol 7: 355-366.

36. Lambris JD, Ricklin D, Geisbrecht BV (2008) Complement evasion by human pathogens. Nat Rev Microbiol 6: 132-142.

37. Yilmaz O (2008) The chronicles of Porphyromonas gingivalis: the microbium, the human oral epithelium and their interplay. Microbiology 154: 2897-2903.

38. Pussinen PJ, Alfthan G, Jousilahti P, Paju S, Tuomilehto J (2007) Systemic exposure to Porphyromonas gingivalis predicts incident stroke. Atherosclerosis 193: 222-228.

39. Darveau RP (2010) Periodontitis: a polymicrobial disruption of host homeostasis. Nat Rev Microbiol 8: 481-490.

40. Hajishengallis G, Wang M, Harokopakis E, Triantafilou M, Triantafilou K (2006) Porphyromonas gingivalis fimbriae proactively modulate beta2 integrin adhesive activity and promote binding to and internalization by macrophages. Infect Immun 74: 5658-5666.

41. Ricklin D, Hajishengallis G, Yang K, Lambris JD (2010) Complement: a key system for immune surveillance and homeostasis. Nat Immunol 11: 785-797.

42. Amano Y, Komiyama K, Makishima M (2009) Vitamin D and periodontal disease. J Oral Sci 51: 11-20.

43. Tang X, Pan Y, Zhao Y (2013) Vitamin D inhibits the expression of interleukin-8 in human periodontal ligament cells stimulated with Porphyromonas gingivalis. Arch Oral Biol 58: 397-407.

44. Na S, Ma Y, Zhao J, Schmidt C, Zeng QQ, et al. (2011) A Nonsecosteroidal Vitamin D Receptor Modulator Ameliorates Experimental Autoimmune Encephalomyelitis without Causing Hypercalcemia. Autoimmune Dis 26: 132958.

45. Weidlich P, Cimões R, Pannuti CM, Oppermann RV (2008) Association between periodontal diseases and systemic diseases. Braz Oral Res 22 Suppl 1: 32-43.

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