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REVIEW ARTICLE

The role of acquired host immunity in periodontal diseases

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Abstract

The aim of this narrative review is to relate the contribution of European researchers to the complex topic of the host immune system in periodontal disease, focusing on acquired immunity. Other chapters in this volume will address the genetics and autoantibody responses and other forms of immunity to periodontal disease. While the contribution of European authors is the focus, global literature is included in this descriptive narrative for contextual clarity, albeit many with European co-authors. The topic is relatively intense and is thus broken down into sections outlined below, tackled as descriptive narratives to enhance understanding. Any attempt at a systematic or scoping review was quickly abandoned given the descriptive nature and marked variation of approach in almost all publications. Even the most uniform area of this acquired periodontal immunology literature, antibody responses to putative pathogens in periodontal diseases, falls short of common structures and common primary outcome variables one would need and expect in clinical studies, where randomized controlled clinical trials (RCTs) abound. Addressing 'the host's role' in immunity immediately requires a discussion of host susceptibility, which necessitates consideration of genetic studies (covered elsewhere in the volume and superficially covered here).

KEYWORDS
acquired immunity, antibodies, cellular immunity, humoral immunity, lymphocytes

1 | INTRODUCTION TO SUSCEPTIBILITY

Epidemiological studies have consistently indicated that the experience and extent of periodontal disease increases with age and inadequate oral hygiene and is predominantly clustered in a sub-group of the population. The analyses of the extent and severity of periodontal disease have informed our understanding of the prevalence and progression of destructive periodontal disease. Few subjects, proportionally, in each age group suffer from advanced periodontal destruction and these subjects account for most severely affected sites in the population with periodontitis.[1–3] Thus only a few individuals experience advanced periodontal destruction and the progression of the disease continues via episodes of exacerbation and remission. The factors creating this susceptible subset are many and both genetic and environmental factors have to be considered. The immune response is clearly a potential effector of susceptibility, whose characteristics depend on genes and environmental exposure, and is thus relevant to periodontal disease susceptibility.

Genome-wide association studies (GWAS) data and other genetic associations are covered in a separate chapter of this volume but to summarize, the data is not strong in pointing at adaptive immune elements,[4,5] if one was to contrast that with the strong GWAS associations seen in say Rheumatoid Arthritis where T cell MHC aspects are associated.[6–8] This is not to say that there is no strong genetic association as these associations are not always unpicked by these genetic studies, and associations can be reliant on gene–gene and gene–environment interactions that are complex to unmask.

2 | THE IMMUNE OR ADAPTIVE DEFENSE SYSTEM

The hallmark of adaptive immune responses is 'specificity' and is predicated on specific antigen–antibody interaction with the host specificity supplied by both the cellular and humoral immune responses (Figure 1). In periodontal disease, antibodies are directed against particular oral microorganisms which may play a decisive role in the development of gingivitis and periodontitis.[9] Microorganisms in the biofilm may provoke an immune response but not fulfill other aspects of Socransky's extended Koch's postulates.[10] Keystone pathogens or species such as *Porphyromonas gingivalis* require particular attention because of the extensive literature implicating them in the etiopathogenesis of periodontitis.

2.1 | Local versus systemic immune responses

We should consider whether local antibody levels in the gingival crevicular fluid (GCF), saliva or in serum, or both, are of importance; or whether local levels are merely a reflection of serum levels, and if significant antibody production by gingival plasma cells occurs. This would be important in the determination of subject and site susceptibility to disease onset and progression.

3 | ANTIBODY SUBCLASSES

The subclass of the immunoglobulin produced has a bearing on aspects of its function such as complement fixation and opsonization (Figures 2 and 3). Certain studies have reported a preponderance of IgG2 production over IgG1 in localized aggressive periodontitis.[11,12] This means that the functionally (binding strength or avidity) less effective IgG2 may have some role in rendering these patients more susceptible to periodontal tissue destruction. Several European studies suggest that assessments of the titre and avidity (the binding strength) of patient's antibody to various microorganisms in the subgingival biofilm may be useful in the differential diagnosis and classification of periodontal diseases.[13]

IgG has four subclasses and IgA has two subclasses. Antibodies of different subclasses have different properties. Thus, IgG2 antibodies are effective against carbohydrate antigens (LPS) whereas the other subclasses are mainly directed against proteins. Kinane et al.[14] studied the immunoglobulin subclasses (IgG1-4 and IgA1-2) produced by plasma cells in the gingival lesion of periodontitis patients. The proportions of plasma cells producing IgG and IgA subclasses were similar to the proportions of these immunoglobulin subclasses in serum. IgG1-producing plasma cells were predominant (mean 63%) in the gingival. 23% of all IgG-producing plasma cells produced IgG2 antibodies, while IgG3 and IgG4-producing cells were present in much smaller numbers (3% and 10%, respectively). Similar proportions of IgG subclass proteins were detected in the crevicular fluid of the same patients.

4 | THE CELLULAR IMMUNE RESPONSE

Generally, cell-mediated immunity is initiated when antigen from subgingival plaque penetrates the connective tissue through the junctional epithelium (Figure 4). Antigen-presenting cells, such as the Langerhans cells (LCs) and dendritic cells (DCs) within the oral mucosa,[15–17] are activated via engagement of their TOLL-like receptors (TLRs) or other pattern recognition

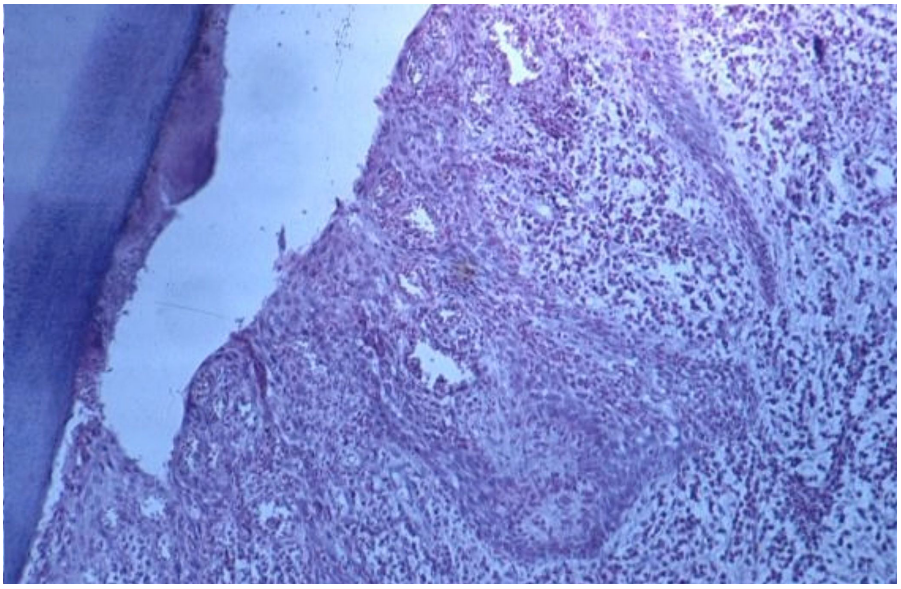

FIGURE 1 Histopathological view of Periodontaldisease, focused on the subgingival region showing the tooth and diseased junctional epithelium, demonstrating inflammatory and immune cell infiltration, including lymphocytes and plasma cells.

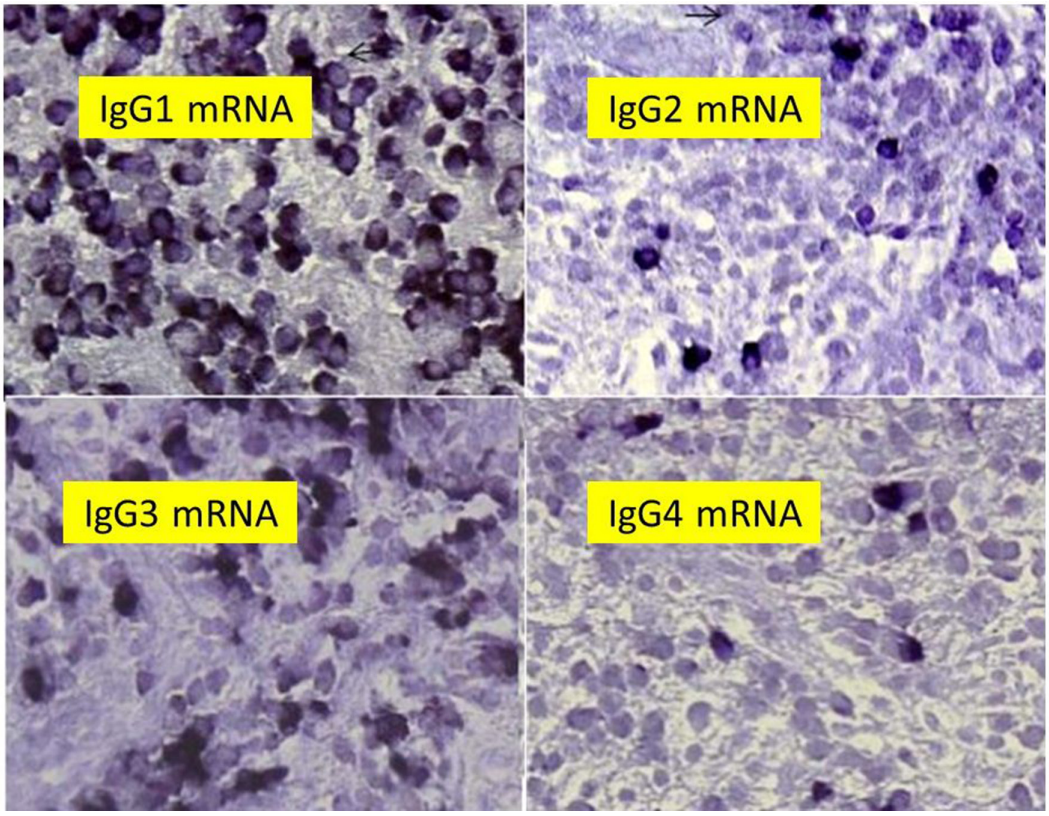

FIGURE 2 Plasma cell subsets in periodontitis (IgG subclasses, a prominent feature of systemic immune response).

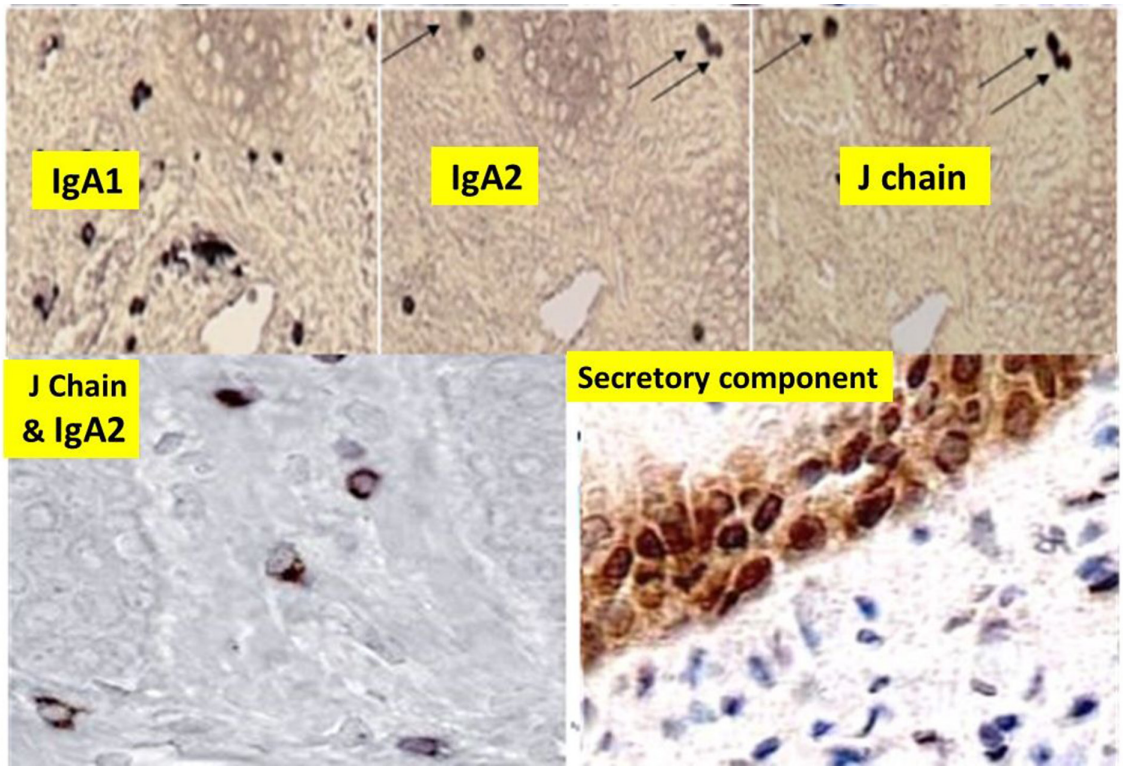

FIGURE 3 Plasma cell subsets in periodontitis (IgA classes, a prominent feature of mucosal immune response).

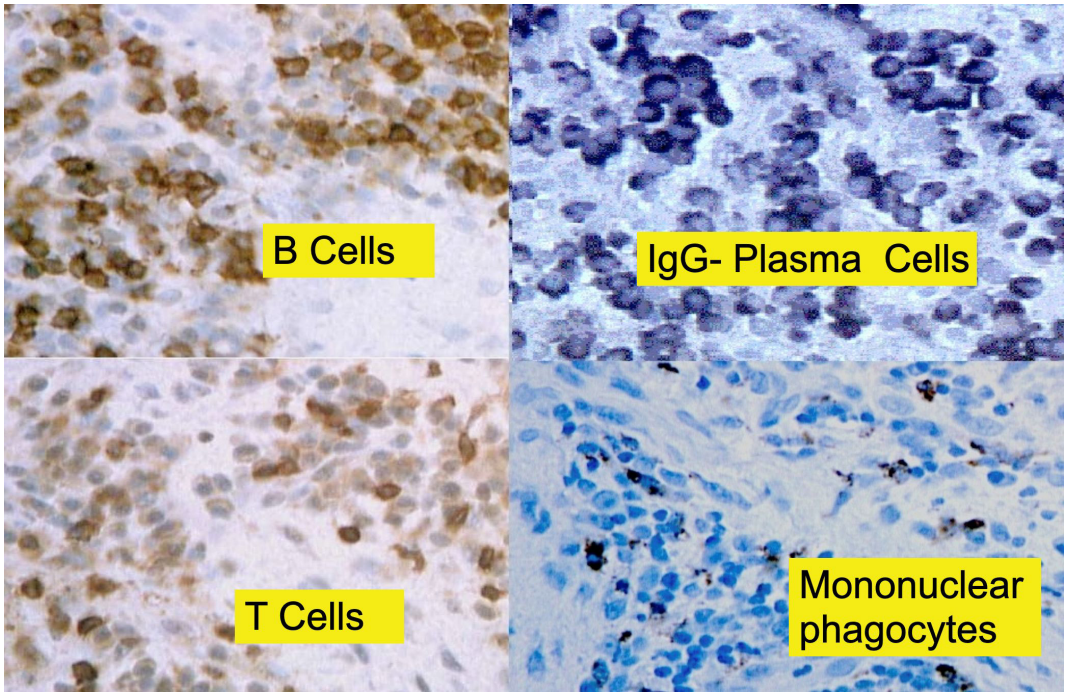

FIGURE 4 Leukocytes in periodontitis lesions.

receptors with microbial surface molecules or bacterial products (antigen) at which point LCs they ingest and process the antigen and alter it to a form that is recognizable by the immune system i.e. the antigenic peptide which binds to the class II major histocompatibility complex (MHC). The T-helper cells recognize this binding between the foreign antigen and the self MHC and become stimulated. The T-helper cells proliferate and release cytokines. However T cell proliferation does not appear to occur to any great extent at diseased periodontal tissue sites but at some other location, such as in the lymphoid tissues.[18] The chemokines and cytokines that are produced locally in inflamed tissues facilitate recruitment and provide activating signals, respectively, for other cell types (i.e., macrophages, B-cells, and other T-cells) to stimulate, inhibit, or even kill microbes or infected host cells. Through this action inflammation, and tissue damage may result.[19,20]

5 | SPECIFICITY OF THE LOCAL IMMUNE RESPONSE

Our understanding of the humoral immune responses of the periodontium is incomplete, it is unclear whether the plasma cells of the gingival tissue produce relevant antibodies to the microorganism within the oral biofilm. It is possible that Langerhans cells and other antigen-presenting cells trigger humoral immune responses within peripheral lymph nodes and that the antibodies produced in the lymph nodes arrive at the gingiva to begin their function. It is also possible that a homing mechanism, and/or a local proliferation of B cells into periodontally relevant plasma cells, within the gingival tissue can occur.[21] Recruitment of leukocytes into areas of injury or infection is essential for host defense (Figure 5). The constant migration of T cells and other leukocytes to sites throughout the body allows the immune system to protect the tissues from a variety of antigenic challenges. Chemokine or chemoattractant-induced leukocyte migration into tissues is particularly prominent during inflammatory responses and results from the cytokine-induced expression of adhesion molecules on the surface of vascular endothelial cells[22] much enhanced during inflammation.

6 | SPECIFIC ANTIBODY RESPONSES

P. gingivalis is considered to be an important pathogen in periodontal disease. Several studies have demonstrated that the antibody titers to this organism is increased in patients with periodontitis compared with subjects without disease.[23–25] Furthermore, Naito et al.[26] and Aukhil et al.[27] demonstrated that the serum titer of antibodies to *P. gingivalis* was reduced in subjects with advanced periodontitis following successful treatment.

Mooney et al.[28] reported on specific antibody titer and avidity to *P. gingivalis* and *A. actinomycetemcomitans* in Chronic periodontitis patients before and after periodontal therapy. The authors observed that IgG avidities (the binding strength of the antibodies) to *P. gingivalis* increased significantly and specific IgA levels more than doubled as a result of treatment. Interestingly, only patients who had high levels of antibody before treatment showed a significant increase in antibody avidity. In addition, patients who originally had high levels of IgG and IgA to *P. gingivalis* also had better treatment outcomes – in terms of a reduced number of deep

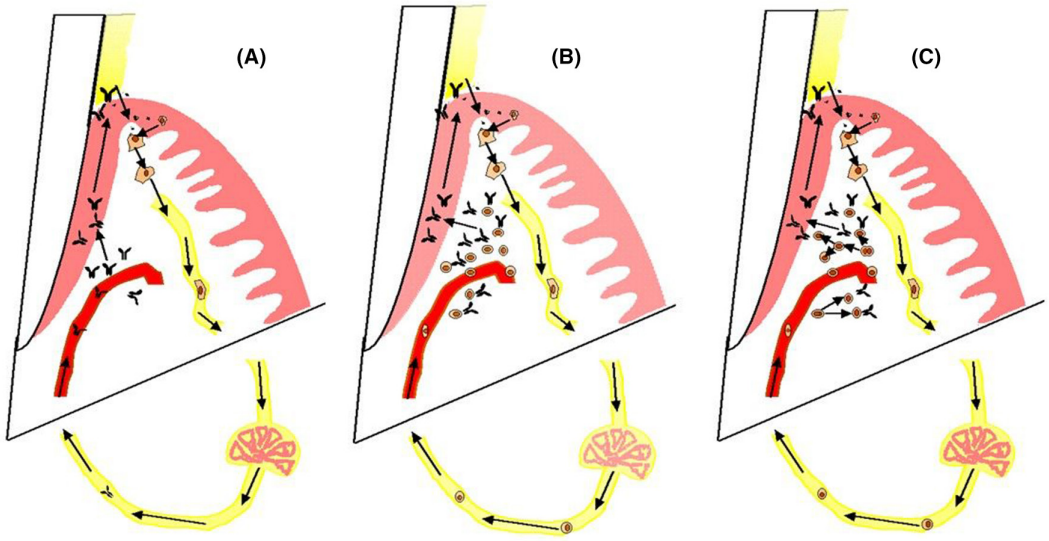

FIGURE 5 Induction of immune response, (A) natural antibodies and antibodies to previous infections, (B) Recruitment of antibody producing cells and local antibody production, (C) Local proliferation of B cell progeny and antibody production. The predominant response, A, B or C, is still to be determined for individuals, individual sites and from a timing perspective and is likely to differ and potentially be a combination of all three of these responses.

pockets and sites that bled on probing – than patients with initially lower titers.

Initial serostatus (i.e., antibody levels) is probably dependent on a number of factors including previous exposure to the subgingival microbiota and the host's ability to respond to a particular antigen. The effect of treatment on antibody level and avidity may be the result from an inoculation (transient bacteraemia) effect that occurs during scaling and root planing. The reduction in the amount of bacteria, i.e. the antigen load, which occurs after subgingival scaling and root planing, results in the activation of B-cell clones that produce antibodies of high avidity (binding strength). Antibodies that bind strongly to antigens are considered fitter and thus more capable of immune host defense function.

These findings described above suggest that periodontal therapy affects the magnitude and quality of the humoral immune response to periodontal pathogens, that this effect is dependent on initial serostatus, and thus, initial serostatus may have a bearing on treatment outcome.

The humoral immune response, especially IgG and IgA, is considered to have a protective role in the pathogenesis of periodontal disease but the precise mechanisms are still unknown. Periodontal therapy itself, may improve the magnitude and quality of the humoral immune response through a process of local gingival immunization.

7 | IMMUNE REGULATION PROCESSES

The host response to factors released by microbial plaque in periodontal diseases involves a series of different effector mechanisms that are activated by the innate immune response. The effector mechanisms, particularly the generally non-specific inflammatory response, in this line of defense may be insufficient to eliminate a given pathogen (e.g., *P.gingivalis*). The adaptive immune response, which is a subsequent and more tailored line of defense, is then activated. The adaptive response improves the host's ability to recognize the pathogen and thus mounts a strong defensive challenge.

Immune memory and clonal expansion of immune cells are hallmarks of adaptive immunity. Although the effector mechanisms activated by the adaptive system appear to be similar to those of the innate system, the anti-microbial activities in adaptive immunity are specialized functions regulated by lymphocytes. This means that the defense mechanisms in the gingiva are synchronized by the communication through signals (cytokines) between specific groups of cells.

The cell types involved in the adaptive response and which reside in the inflammatory lesion in sites with periodontitis have been described in several European studies that included a histopathological analysis of the tissue composition.[29–34] It was observed that plasma cells and lymphocytes were the most common cell types in the lesions and that they occupied similar volumes of the inflammatory cell infiltrate. The lymphocytes in such lesions were further divided into T cells and B cells and it was reported that also T cells and B cells occurred in similar proportions. The following outline provides an overview of T cell and B cell characteristics and immunoregulatory mechanisms of importance in periodontitis.

8 | T CELL IMMUNITY

As discussed above, patients with periodontitis generate antibodies specific for bacteria in the biofilm – although the role of these antibodies is not clear – their presence clearly indicates the adaptive immune response in periodontitis. T lymphocytes are central to this

adaptive immunity and among their myriad other roles, CD4 T cells[35] provide help for B cells to generate specific antibody. T cell activation requires engagement of the T cell receptor with cognate antigen in the context of MHC, along with co-stimulatory signals – generally provided by the antigen-presenting cell. The T cell activation is further nuanced by the cytokine milieu. The adaptive T cell response can be considered to include CD4 (T helper) or CD8 (cytotoxic) T cells, each of which has been characterized into subsets, such as Th1, Th2, Th17, various T regulatory types.[36–42] These T cells have T cell receptors which are specific for a particular antigen. Estimates suggest that about one in one hundred thousand T cells will recognize any given foreign antigen – antigen-specific cells are rare, and in total approximately 100 naïve T cells out of the total T cell pool might recognize a given peptide:MHC complex.[43,44] Therefore, T cell cross-reactivity with more than one peptide:MHC complex is essential.[45] The roles of T cells span the boundaries of adaptive and innate responses. There are groups of T cells that appear to have minimal specific antigen dependence for example, Innate lymphoid cells (ILCs), γ/δ T cells, and mucosa-associated lymphoid tissue (MALT) cells. Although these T cells have T cell receptors (TCRs), their recognition of conserved epitopes appears to play a key role their function.

9 | GENETIC STUDIES INFER A ROLE FOR ADAPTIVE IMMUNITY

One third of the population variance in periodontitis is estimated to be due to hereditable factors, and this hereditability appears most evident in severe forms.[6] Hereditability and genetics are explored in detailed in this issue, and so are considered here only in the context of the adaptive response. In other inflammatory disease such as rheumatoid arthritis, host response genes are consistently and strongly associated with disease. In periodontitis, most data suggest some elements of host response are involved in hereditability. However, there are limited data implicating T and B cell responses. In conditions, such as rheumatoid arthritis, large scale Genome-Wide Association Studies (GWAS) data sets clearly point to associations with MHC Class II (the 'shared epitope' Class II allele – HLADRB1*401) and components of T cell activation (such as PNTP22) – thereby implicating T cell responses.[4,6,7] Some HLA associations, including the shared epitope. have been reported in periodontitis, but with relatively small cohorts and relatively weak associations, suggesting the Class II association is not as clear cut and meta-analysis of HLA associations in periodontitis revealed no association with variations in MHC Class II.[46] Some GWAS studies of periodontitis have indicated associations with sialic acid binding immunoglobulin like lectin 5 (SIGLEC5) – a T cell inhibitory pathway, which may suggest a role of T cells in human periodontitis.[6,47,48] Future studies, such as the 'Gene-lifestyle interactions in dental endpoints' ('GLIDE') consortium will shed further light on these associations.[49] Dysfunction of neutrophils is linked to heritable polymorphisms of antibody receptors (Fcγ R) and affects the ability of phagocytic cells to fix immune complexes, etc., and are associated with aggressive forms of periodontal disease.[50,51]

10 | DIFFERENCES IN CIRCULATING T CELLS IN PERIODONTITIS VS HEALTH

Changes in T cells have been observed in the circulation and in the periodontal tissues. A recent metanalysis of ten studies demonstrated elevated circulating CD4 T cells in patients with periodontitis versus periodontally healthy controls, and a small but significant reduction in numbers of circulating CD8 T cells. Both the circulating CD4 and CD8 T cells showed elevated expression of IFN-γ in periodontitis patients compared with healthy. IL-17A expression in the CD4 cells varied between studies and overall, no difference was identified between healthy and periodontitis patients CD4 cells from patients with periodontitis had a tendency to show elevated proliferation when stimulated with antigens from periodontitis associated bacteria. There were minimal differences in γ/δ circulating T cells in periodontitis vs health.[52]

11 | EFFECT OF TREATMENT ON CIRCULATING T CELLS

The autologous proliferative response has been reported to increase after periodontal treatment.[53] Berglundh et al.[54] characterized TCR usage before and after periodontal treatment[54] and found that of thirteen different Vβ chains evaluated, only the use of Vβ22 reduced after treatment. Periodontal treatment resulted in reductions in circulating Th17 cells.[55]

12 | T CELLS IN THE GINGIVAL TISSUES IN PERIODONTITIS

Comparisons between the gingival lesions in periodontitis and health, and between the gingival T cells and circulating T cells consistently demonstrate selective T cell recruitment to the gingival tissues, and changes in the T cells in the tissues in health compared with periodontitis.

A series of studies by and Liljenberg et al.[30,31,54,56–58] demonstrated that around 10%–15% of the inflammatory infiltrate in advanced stage periodontitis lesions consists of CD4 T cells, which are predominantly CD45RO memory cells. The proportion of CD8 cells is somewhat less.[57] The cytokine profiles of these CD4 cells appears to be quite heterogeneous with IFN-γ, IL-6, IL-17A expressing cells all identified.[59] Whether the proportions of T cells (and B cells) significantly changes in periodontitis and health is not consistently identified, with some studies showing similar proportions of CD4 cells (as total CD45 leukocytes) in periodontitis compared with health.[60] Given the size of the inflammatory infiltration/lesion is increased the total numbers of all cell types seems inevitably increased. IL-17A

is produced principally by IL-23 stimulated T cells,[61] and the most consistent and striking seems to be an increase in the proportion of IL-17A expressing CD4 T cells in periodontitis in disease compared with health.[60] This differential in IL-17A expression appears limited to the CD4 compartment – with CD8, γ/δ and ILC populations showing similar IL-17A expression in health vs disease. Determining the specificity of these cells has proved challenging. The use of the V Beta chain is different in circulation compared with in the tissues, suggesting a selective recruitment of antigen specific cells into the tissue.[54]

More recently, single RNA sequencing approaches have provided further insights into the immune cell components of the gingival tissues. RNA analysis of tissues suggests that diverse forms of cell populations are in involved in periodontitis. In these studies, there is evidence that the T cell component may be more dominant in health than disease.[62]

13 | FUNCTION OF T CELLS IN PERIODONTITIS

While observations of differences in health and disease and in changes after treatment imply a role for T cells in periodontitis, exploring their function is challenging. Studies of patients in whom T cell function is compromised yield somewhat inconclusive results. Studies of periodontal health in HIV positive patients suggest an association with periodontitis, CD4 count and age. Compared with HIV seronegative controls, HIV-seropositive patients are more frequently diagnosed with necrotizing periodontitis.[63,64] Such atypical periodontal diseases generally associated with declining CD4 counts. Therapies that protect the CD4 counts appear to protect against periodontal disease. Combined antiretroviral therapies (cART) have been in use for over two decades and studies in cohorts of these patients show that patients on these therapies tend to have similar periodontal health to HIV negative controls. Surprisingly, some studies show that even cART non-compliant patients who show increased viral load only show a marginal increase in tooth loss. Ongoing studies in young people – perinatally infected or uninfected may reveal the subtleties of effects.

Several immune suppressive treatments – particularly those used in preventing rejection of organ transplants – target T cell. For example cyclosporin A (CsA), inhibits calcineurin and prevents translocation of the cytosolic component of nuclear factor of activated T cells (NFAT), and inhibits production of IL-2[65] – essential for T cell expansion.[66] CsA has complex effects on T cell activation – in general inhibiting activation induced cell death (hence protecting the transplant) but also inhibiting induction of regulatory T cells. Transplant patients receiving CsA treatment frequently suffer gingival overgrowth. Drugs such as tacrolimus (FK506), mycophenolate and rapamycin (Sriolumus) are commonly used in transplant patients and target T cell functions. Aside from the well documented relationship between gingival overgrowth and cyclosporin, there appears to be minimal impact of cyclosporin on periodontal attachment loss.[67] However, a comparison of periodontal status in patients taking tacrolimus, cyclosporin and sirolimus (rapamycin) demonstrated a small but statistically significant increase in periodontal pocket probing depths and attachment levels only in patients taking cyclosporin.[68] These are challenging studies in complex patients and controlling for all confounders is almost impossible – but just as studying periodontitis in monogenic diseases[69,70] has rapidly expanded our understanding, studies of patients taking the ever-increasing array of immune modulatory drugs will be key to understanding the immune response in periodontitis. To date, however, therapeutic T cell targeting, or infection mediated deficiency in humans has yet to shed much light on the roles of the adaptive immune response in periodontitis. Therefore, most mechanistic, and functional data are from animal studies.

14 | ANIMAL STUDIES OF T CELL FUNCTION IN PERIODONTITIS

The negligible impact on periodontal bone loss following treatment with cyclosporin and tacrolimus observed in humans was mirrored in animal studies.[71,72] By contrast, studies of Severe combined immunodeficiency (SCID) mice which are completely deficient in both T and B cells (as their genetic deficiency renders them unable to make B or T cell receptors) show that the adaptive response appears to play a destructive role in periodontitis; SCID mice show less bone loss following infection with *P.gingivalis* than normal mice.[73,74] The destructive role of T cells was further supportive by experiments in which adoptive transfer of T (CD45RBhi) cells into SCID mice resulted in alveolar bone loss.[75] CD8+ T cell and NK T cell knockout mice showed no significant change in bone loss after oral infection.[76] The contribution of T cell cytokines has been explored using cytokine gene knock out mice. IFN-γ knock out mice appeared protected from bone loss following oral infection with *P.gingivalis*.[76] However, in another mouse model, infection of IFN-γ deficient mice with *Aggregatibacter actinomycetemcomitans* resulted in increased fatality.[77] These data suggest that the archetypal Th1 cytokine may be both protective and destructive depending on context. Murine studies abrogating IL-33 – a Th2 cytokine – suggest that IL33 promotes alveolar bone loss.[78] The Th1/Th2 balance[79,80] appears to have limitations in explaining periodontal disease processes.[41]

Early studies of Th17 responses showed conflicting results. Mice deficient in IL-17RA show increased bone loss following oral infection with *P.gingivalis*. In this model, IL-17A dependent neutrophil recruitment to infected gingival tissue was imperative for defense against bacterial infection. Hence IL-17A deficient mice show reduced recruitment of neutrophils to the inflamed gingival tissue and increased bone loss.[81] Conversely, Del-1 deficient mice revealed a role for the IL-17 family of cytokines (mainly IL-17A, IL-17F homodimers and IL-17A/F heterodimers) in promoting bone destruction. IL-17A inhibits Del-1 expression, thereby promoting neutrophil recruitment; and in this setting the neutrophil recruitment appears to be more destructive than protective.[82] The plasticity and subtleties

of Th17 responses have been revealed over time, and 'fate maping' (whereby animals are genetically modified so that any cells that express IL-17A are irreversibly fluorescently labeled) experiments show that T cells are capable of 'trans differentiation' in the context of chronic microbial infection and inflammation. – and thus Th17 cells can change their function at different stages of *P.gingivalis* infection.[83] T cell derived IL-17A has been shown to play a key role in osteoclastogenesis in periodontitis[84,85] and drive tissue damage and is elevated in periodontitis.[86,87] IL-17E (IL-25) antagonizes many of the functions of IL-17A, IL-17F and other family members by promoting Th2 cell functions inducing IL-4, IL-5 and IL-13 gene expression.[88] Inflammatory[86,89] and ani-inflammatory forms of IL-17 are expressed and detected in periodontitis lesions[86] and in crevicular fluid.[86] Animal studies have demonstrated the protective role of regulatory T cells in periodontitis – Inhibiting Treg function by targeting glucocorticoid-inducible tumor necrosis factor receptor (anti-GITR) exacerbated disease with increased alveolar bone loss and increased influx of inflammatory cells.[90,91] Administration of C-C motif chemokine ligand 22 (CCL22) recruited Tregs to gingival tissues, decreasing inflammation and reducing alveolar bone loss.[92] Phenotypic and functional analysis of Tregs during a model of periodontitis suggest that periodontitis may render T regs ineffective – thus negating their potential to regulate bone loss.[93]

The role of γγ/δ T cells has been explored in animal models (although there are marked differences in the γγ/δ compartment in mice versus humans). Recent data show that absence of γγ/δs in the ligature model had no impact; however, absence of γγ/δs in the *P.gingivalis* oral gavage model resulted in protection against alveolar bone loss, suggesting that like CD4 cells, in some contexts, γγ/δs may be destructive.[94] Gamma Delta T cells may be protective and promote barrier integrity and their absence resulted in greater age and ligature related bone loss in mice.[95]

15 | T CELL SPECIFICITY IN PERIODONTITIS

The precise antigen specificity of T cells in periodontitis remains to be elucidated. As previously noted, the T cells present in the gingival tissues are distinct from those in the circulation, implying that selection and recruitment, possibly based on antigen specificity has occurred. MHC tetramers has allowed identification of antigen specific T cells in RA.[96] This is a challenging technique in multifactorial inflammatory human disease, as it requires identification of peptide antigen and HLA-typing of patients. To date, tetramers have successfully been developed to track *P.gingivalis* specific memory/effector T cells in the murine model of periodontitis.[97] Molecular means of determining single cell T cell antigen specificity will be crucial to identifying antigen-specific memory T cells infiltrating periodontal tissues and elucidating their function. The inflammation of periodontitis will create a chemokine milieu conducive to recruiting all leukocytes; however, the selection and expansion of T cells that come to reside in the gingivae (both in health and disease) requires a tissue homing signal. 'Address codes' that bring T cells to the gut are well defined but the specific homing signal to the oral mucosa (that will recruit T cells in health as well as inflammation) is not yet known. Within the periodontal tissues (in health) there is high expression of the chemokine CCL19, typically responsible for regulating recruitment of Chemokine receptor (CR)7 expressing cells to secondary lymphoid organs, the specific function of this in gingiva is unknown.[62,98] In addition to migrating into tissues T cells can migrate out of the tissues and into other sites. This has implications for links between periodontitis and systemic diseases. Recent studies show that Th17 cells from the gingivae can migrate to the gut and mediate inflammatory damage in the gut.[99]

16 | THE TCR REPERTOIRE

It is well known that the composition – or expression – of the variable chains of TCR – TCR γ/δ phenotype or genes – is of importance in several autoimmune diseases and also in periodontal disease.[30,31,100–102] The results reported on TCR in periodontitis have consistently revealed that the TCR repertoire of T cells in the local periodontitis lesions differs from that of T cells in peripheral blood. In other words, factors present at the local site, i.e. antigens released from microorganisms in the subgingival biofilm, may influence the expression of TCR in the periodontitis lesion.[100,103,104] This fact also explains the differences observed in the distribution of TCR in gingival tissues (i) before and after periodontal therapy[54] and (ii) between adult subjects with advanced chronic periodontitis and children with aggressive periodontitis.[58]

16.1 | T cell dependent processes

Cytokines produced by T-helper (Th) cells regulate most systems within adaptive immunity of periodontal disease. T helper cells occur as Th-1, Th-2 cells and other Th subsets (Th9, Th17, Th22, Tfh and Treg cells). These Th subsets that all express the CD4 marker but are distinguished from each other by their cytokine production.[105] Cytotoxic T cell subsets (Tc1, Tc2, Tc9, Tc17 Tc22, etc.) express the CD8 marker, also distinguished by cytokine profile, serve as guards against microorganisms that are capable of invading host cells, i.e. virus and invasive bacteria. In the infected host cells the antigen (peptide) produced by the intracellularly located pathogen binds to MHC class-I molecules which carry the peptide to the surface of the infected host cell. The cytotoxic T cell has the ability to recognize this alteration in the MHC class-I molecules and exerts its host defense action by destroying the cell membrane of the infected host cell and by activating its nucleases. This cell-mediated host response orchestrated by the Tc also includes activation of macrophages. T cell products also include receptor activator of nuclear factor-kappa B ligand (RANKL) a major stimulator of macrophages and osteoclasts.[106] RANKL promotes tissue destruction but is diverted from the receptor RANK by the surrogate receptor for RANKL osteoprotegerin

(OPG). The balance between RANKL and Osteoprotegerin (OPG) members of the TNF family and TNFR family of cytokines, in tissue fluids and the circulation and their association with the destructive processes in periodontal diseases have been studied in detail.[107,108]

17 | B CELL REGULATION PROCESSES

The large amounts of soluble and accessible antigens occurring in the periodontal environment require the involvement of host defense systems different from those involved in cell-mediated immunity. Specific antibodies (immunoglobulins), occurring in fluids such as plasma or gingival crevicular fluid, have the ability to bind to the antigen. This type of host defense is called humoral immune response. By the process of binding to the antigen the antibody activates different effector systems, e.g. complement. The activation of the complement system in turn mediates PMN and macrophage migration and phagocytosis. The process in which the antibody contributes to the elimination of antigens by enhancing phagocytosis is termed opsonization (Figure 6).

Antibodies are produced by plasma cells that represent the final stage in B cell activation and proliferation. The activation and differentiation of B cells require the presence of certain cytokines – IL-4, IL-5, IL-6 – that are mainly produced by Th2 cells[109] and other B cell activating factors: B-cell activation factor (BAFF) and a proliferation-inducing ligand (APRIL)[110] members of the TNF family of cytokines. Early investigations appear to show that plasma cells and B cells constitute a major part of the leukocytes in advanced periodontitis lesions it was reasonable to assume that Th-2 functions may dominate over those dependent on Th1. In early studies it was indeed suggested that the immunoregulatory mechanisms in the advanced periodontitis lesions involve Th-2 cells to a larger extent than Th1 cells.[111,112] Several later studies have, however, failed to confirm this observation.[102,113–116] Current data thus suggest that chronic periodontitis lesions are regulated by a combination of T helper cell subsets principally Th-1, Th-2 and Th17 cells.[117,118]

In this context it should be recognized that a clinically successful, non-surgical periodontal therapy (i.e., reduction of sites with deep pockets and that exhibited bleeding on probing) failed to alter the proportion of B-1 cells in peripheral blood.[54] It was suggested that the elevated levels of B-1 cells in peripheral blood may not entirely reflect a response to microorganisms in the subgingival biofilm. It has been suggested that the effector systems in the humoral immune response in periodontitis may include production of antibodies harmful to the gingival tissues.[119] While there is little evidence for this in chronic periodontitis, this might occur in aggressive periodontal disease.[120]

18 | HOMING—RECRUITMENT OF SPECIFIC IMMUNE AND CELLS TO THE PERIODONTIUM

The recruitment of leukocytes into areas of injury or infection (homing) is essential for an effective host defense and the constant migration of leukocytes into the inflamed periodontal tissues results

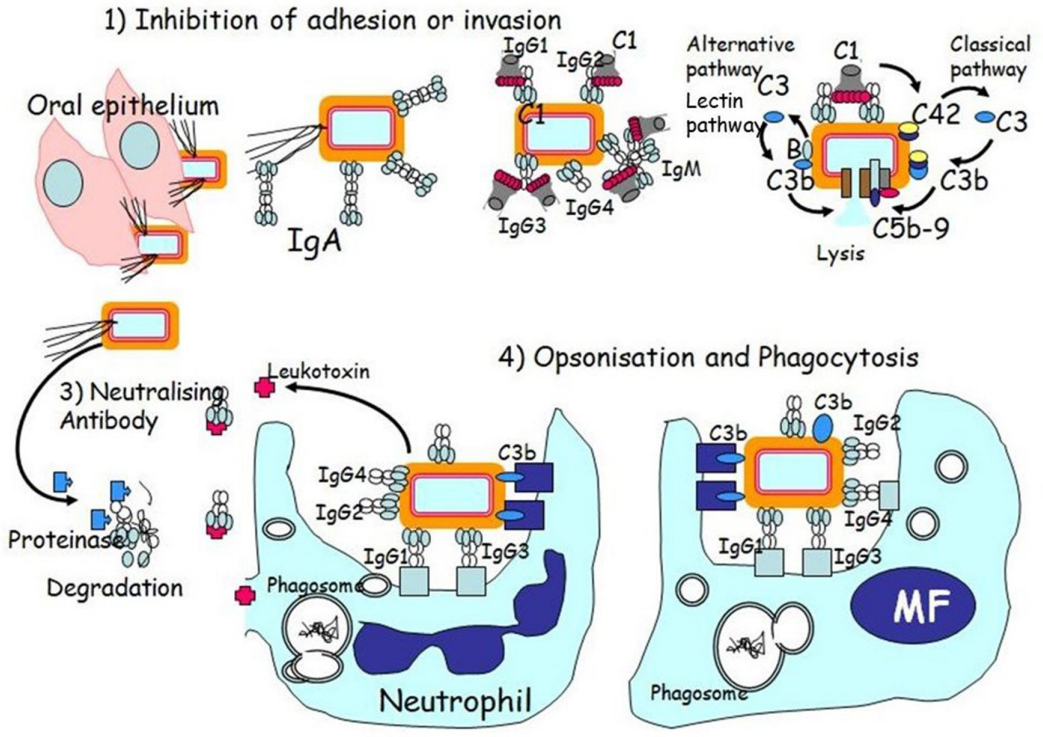

FIGURE 6 Opsonisation by antibody and complement and the specificity of phagocytic cells.

from the cytokine-induced expression of adhesion molecules on the surface of vascular endothelial cells (Figure 5). It has been suggested that Langerhans cells and other antigen presenting cells set up humoral immune response functions within peripheral lymph nodes. Evidence exists, however, that homing of cells involved in both humoral and cellular immune responses is pronounced in diseased periodontal tissues. Thus, local proliferation of such leukocytes seems to play a minor role.[121] In other words, the large number of T-cells and B-cells that occur in the periodontitis lesion are attracted to the diseased site through selective homing and are not the result of local T- and B-cell proliferation. Although selective homing is feasible, the process may combine the non-specific infiltration of immune cells along a chemokine or chemoattractant gradient into inflamed tissue, for example periodontal lesions: 'specific' infiltrating cells may be retained locally after interaction with antigen presenting cells bearing the appropriate configuration for binding to these infiltrating cells. Thus 'homing' of a relevant immune cell population may occur through this mechanism.

19 | THE IMMUNE RESPONSE IN VARIOUS SITES

Regarding the humoral immune response and its important role in periodontal disease most investigations have focused on peripheral blood or GCF with less focus on the local immune response at the site of the lesion. Sampling serum, or even GCF, may not reflect the activity of cells present in the periodontal lesion and gingival tissues.

The major pathological features of periodontal diseases are: (i) apical migration of epithelial attachment; (ii) an accumulation of inflammatory infiltrate within the periodontal pocket tissues; (iii) breakdown of connective tissue fibers anchoring the root to alveolar bone; and (iv) resorption of the marginal portion of the alveolar bone which eventually results in bone loss. The clinical and histopathological stages of health to periodontal disease were systematically defined originally by Page and Schroeder,[122] who developed a classification system to categorize the different stages of the disease process. However, much of this work was carried out on animal and adolescent biopsies, so for this reason the following discussion will use the system published by Kinane,[123] which is based on that of Page and Schroeder and classifies the disease progression from health to advanced periodontal disease. The classification system includes: the pristine gingiva, which is histological perfection; the normal healthy gingiva; early gingivitis; established gingivitis; and periodontitis.

Although Lindhe et al.[124] reported that the cellular infiltrate of diseased tissues is predominantly made up of plasma cells, Wittwer et al.[125] reported that the number of plasma cells was equivalent to or in some cases was exceeded by, the number of lymphocytes. Platt et al.[9] reported that there are approximately 5 times more lymphocytes than plasma cells present. Mackler et al.[126] reported that the cellular profile of the periodontitis tissue biopsies was different from gingivitis biopsies and mainly consisted of immunoglobulin-bearing lymphocytes and plasma cells.

Liljenberg et al.[56] compared plasma cell densities in sites with active progressive periodontitis, and in sites with deep pockets and gingivitis but no significant attachment loss over a 2 year period. The density of plasma cells (51.3%) was significantly increased in active sites compared to inactive sites (31%), indicating that plasma cells are the dominant cell type in the advanced lesion, while different sampling times may have yielded a different result, there is support in the literature for a preponderance of plasma cells in advanced chronic periodontitis lesions.[33,121,127]

Although studies investigating the numbers of immunoglobulin-bearing lymphocytes and plasma cells in the tissues seem to be numerous, it is important to consider the function and target of these cells. The products of B cells include RANKL, which stimulate osteoclasts[128–130] and along with the plasma cells in the tissues include antibodies, which may be active against components and metabolites of periodontal pathogens,[131] which may result in immunopathology and tissues destruction.[128,129,132] Further to this, examination of plasma cells and their targets in the diseased tissues, which are specific to the infection and have undergone affinity maturation and migration to the site, may lead us to a clearer idea of the more important pathogens and immune response inducing antigens.

Several studies using a variety of techniques to investigate local defense mechanisms and their specificity have been carried out over the last few decades. Schneider et al.[133] carried out a study to demonstrate that there is a local defense mechanism, present in gingival tissues, of adults with marginal gingivitis and periodontitis against bacteria removed and labeled with acridine orange from the adjacent sulcus or pocket to the site of the tissue taken. Frozen sections of the biopsies were adhered to glass slides by the warmth of a finger. The first investigation carried out was of the reaction of one of the sections from each biopsy with fluorescein conjugated rabbit anti-human globulin to demonstrate specific staining of immunoglobulins in these diseased gingival tissues. Intense fluorescence was seen predominantly in the connective tissue. Staining was also seen within the cytoplasm of the perivascular plasma cells. The second part of the study utilized further serial sections from the biopsies. The acridine orange stained bacterial suspensions were added to each section and incubated, before washing and the addition of rabbit anti-human globulin globulin conjugated to fluorescein isothiocyanate. in contrast other sections were stained firstly with the fluorescein conjugated rabbit anti-human globulin globulin prior to acridine orange stained bacteria. The results showed that the bacteria reacted with the tissues in areas of high antibody concentration, indicating specific antibody–antigen reactions. The specificity was confirmed by the fact that gingival tissues that had been reacted with rabbit anti-human globulin globulin prior to labeled bacteria the the bacterial reactions were inhibited as the antigen–antibody sites were blocked. In most of the sections observed, individual plasma cells were also seen to be reacting with bacteria. The bacteria could be observed as single cells lined up around the periphery and overlying the cytoplasm of plasma cells. Although, this study showed

that there are potentially specific interactions between antibodies present in the tissues and antigens, the specificity of the bacteria and bacterial targets was not investigated. Many antibodies could be present in the tissues that have migrated in with the exudative fluid during the inflammatory reaction that may not be specific for the bacteria added for the experiment and may have bound to non-specific moieties present on the surface of the bacteria such as lectins. Such interactions are known to occur between some strains of *E.coli* and murine lymphocytes.[134]

20 | SPECIFICITY OF PERIODONTAL PLASMA CELLS

Schonfeld and Kagan[135] determined the percentage of plasma cells in initial and advanced lesions, from sections of gingival tissue biopsies taken from periodontitis patients, that were directed against A. viscosus, strain ATCC 27044 and T14-V, *P.gingivalis* and *A. actinomycetemcomitans*. The methodology used in the study of Kinane & Lappin[18] was as described previously.[136] The results suggested an important role for *P.gingivalis* in the pathology of periodontal disease. Where the binding of various putative pathogens to specific plasma cells was determined. The binding of *P.gingivalis* was seen in all of the advanced lesions, but only in 40% of the initial lesions, and a much higher number of plasma cells in the advanced lesions bound *P.gingivalis*. The low specificity towards the other putative pathogens tested remained unclear. Numerous other studies have indicated that patients with chronic periodontitis possess high titers of serum antibody to *P.gingivalis*[137–140]; therefore, it seems that the specificity of the systemic immune response is reflected locally (or vice versa). These studies support the hypothesis that the majority of specific leukocytes predominate in the periodontitis tissues through selective homing rather than by local proliferation.

21 | FUTURE RESEARCH ON ADAPTIVE IMMUNITY IN PERIODONTAL DISEASE

T cells are indisputably present in both gingival health and periodontitis. In the future, our understanding of these cells will form part of a greater understanding of the immune regulation in the gingivae in both health and disease. No single study modality will answer these fundamental questions. Genome analysis; investigations in patients with monogenic diseases; investigations in patients taking immune modulatory therapies; evaluations in patients with HIV and other infections that target the immune system; evaluation of immune cells in patients with just periodontitis, and different animal models will each yield part of the picture. The challenge will be consolidating and interpreting this wealth of information and translating the findings to promote oral and general health.

Vaccination against periodontal disease? This is considered unlikely at present given that there are multiple (interchangeable?) pathogens involved and not really a single one that could be targeted, despite the prominence of *P.gingivalis* in the literature. Unlikely as it may be, research into *P.gingivalis* nullification by immunization would be immediately useful in confirming this microorganisms pivotal role, and might be a therapeutic target with utility. The argument that other Gram negative bacteria and Spirochaetes would simply take its place, or that mutations would arise, need to be considered.

The conundrum that immunosuppressed have minimal gingivitis and periodontitis needs to be addressed prior to endorsing the pivotal role of the adaptive immune response in periodontal disease. This issue is complicated by the diversity of treatments employed in to treat such individuals, whether these would impact directly on the inflammatory and immune response and thus on the host response to the microbiome or alter the microbiome directly and thus alter the host response or a combination of these, where combine therapies are employed.

The data at present might simply point to the adaptive immune response, cellular and humoral, as being reactive rather than predisposing.

Research using adaptive immune system components as the therapeutic targets for 'drug targeting' and 'precision medicine' approaches will abound into the future and may uncover more information on the relevance and role of specific components of the adaptive immune system in periodontal disease.

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DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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