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Periodontal Microbes and Immunity

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Abstract: *Knowledge of how immune mechanisms and inflammatory responses are regulated is critical for understanding the pathogenesis of complex diseases, such as periodontitis. The pathogenesis of periodontal disease is mediated by the inflammatory response to bacteria in the dental biofilm. Unlike many infectious diseases, periodontal diseases appear to be infection mediated by the overgrowth of commensal organisms rather than by acquisition of an exogenous pathogen. Recent advances in cellular and molecular biology research have demonstrated the importance of the acquired immune system not only in fighting the virulent periodontal pathogens, but also in protecting the host from developing further devastating condition in periodontal infections. Three basic mechanisms have been postulated to play a role in these interactions; metastatic infections, inflammation and inflammatory injury, and adaptive immunity. The potential role of each alone and together is considered in, in vitro and animal studies and in human studies when available.*
The present review is intended tohighlight the emerging role of neutrophil extracellular trap production in the regulation of immune response andits role in periodontal disease.
Keywords: *dental biofilm, adaptive immunity, acquired immune system.*

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I. Introduction:

A great amount of effort and preparation is required prior to a theatrical production. Although the curtains may open to an apparently quiet and inanimate scene, all of the stage-hands, lighting staff, technical crews, actors and musicians know their places on the stage and respond to specific signals during the play.

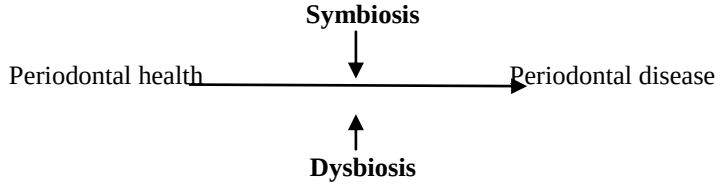
Periodontal health is a dynamic state that may be viewed as one scene in a play. As certainsignals are given, specific players respond in a practicedmanner and take their places in the scene. Ifdisease-initiating signals are given, the players takepositions on the stage that allow them to participatein the disease scene.

Periodontitis is an inflammatory disease induced by bacterial biofilms that accumulate in the gingival margin, in which a series of aberrant inflammatory responses are initiated in periodontal tissues by a small subset of endogenous gram-negative periodontal bacteria, including Porphyromonas gingivalis, Aggregatibacter (Actinobacillus) actinomycetemcomitans, Tannerella forsythia (forsythensis) and Treponema denticola.

However, recent data from metagenomic, metatranscriptomic and mechanistic studies are consistent with a new model of periodontal disease pathogenesis, which suggests that a more diverse periodontitis-associated microbiota is involved in the disease than previously thought. **(Abusleme, L. et al 2002, Hajishengallis, G. et al 2012)**

Understanding how oral pathogens misdirect the host immune response can provide novel mechanistic insights into the pathogenesis of periodontitis and associated systemic conditions, as well as reveal new therapeutic targets.

II. Microbial Synergy And Dysbiosis (Hajishengallis G. 2015)

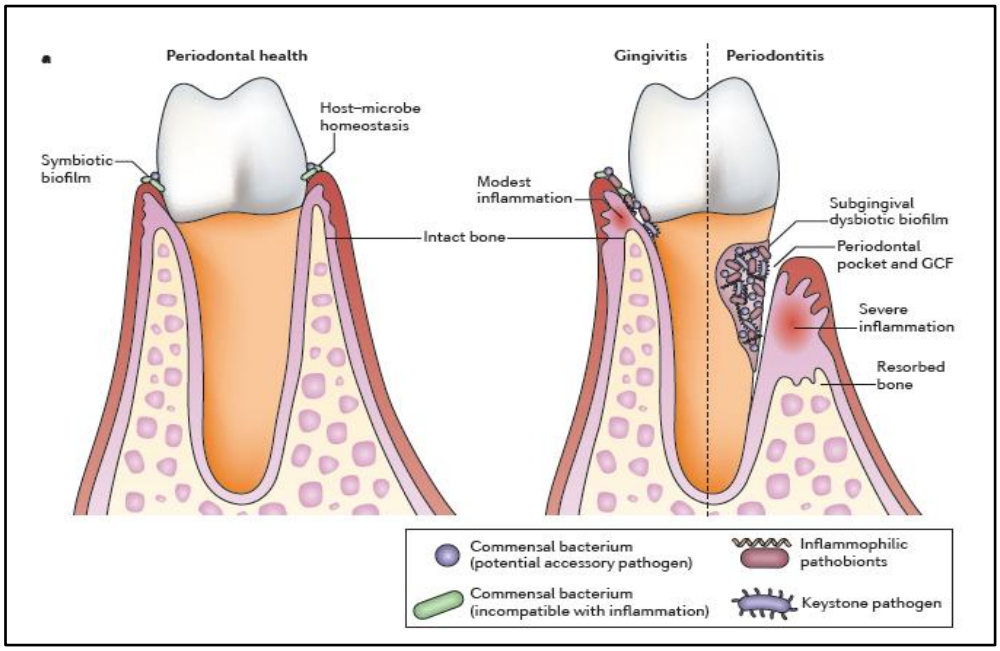


(anaerobic genera from the phyla Firmicutes, Proteobacteria, Spirochaetes, Bacteroidetes)

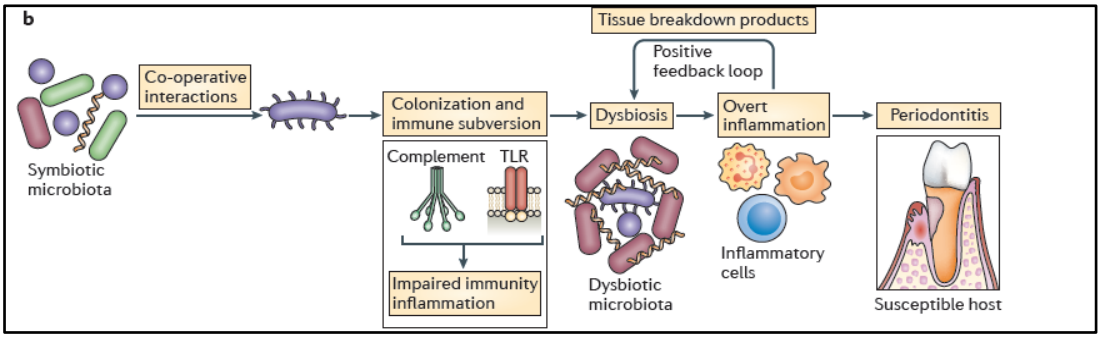
Periodontitis has a complex aetiology that acts at multiple levels:

PERIODONTITIS

MICROBIAL	**HOST**	**SYSTEMIC HEALTH**	**ENVIRONMENTAL**
P. gingivalis	Genetic factors,	Diabetes,	Smoking
A. actinomycetemcomitans	Increased release of IL1, IL6, IL8, TNF, PGE2.	Hormonal imbalance	Stress
T. denticola			
C. rectus,			
B. forsythus			



The figure shows progression from a state of periodontal health, to gingivitis and development of periodontitis.



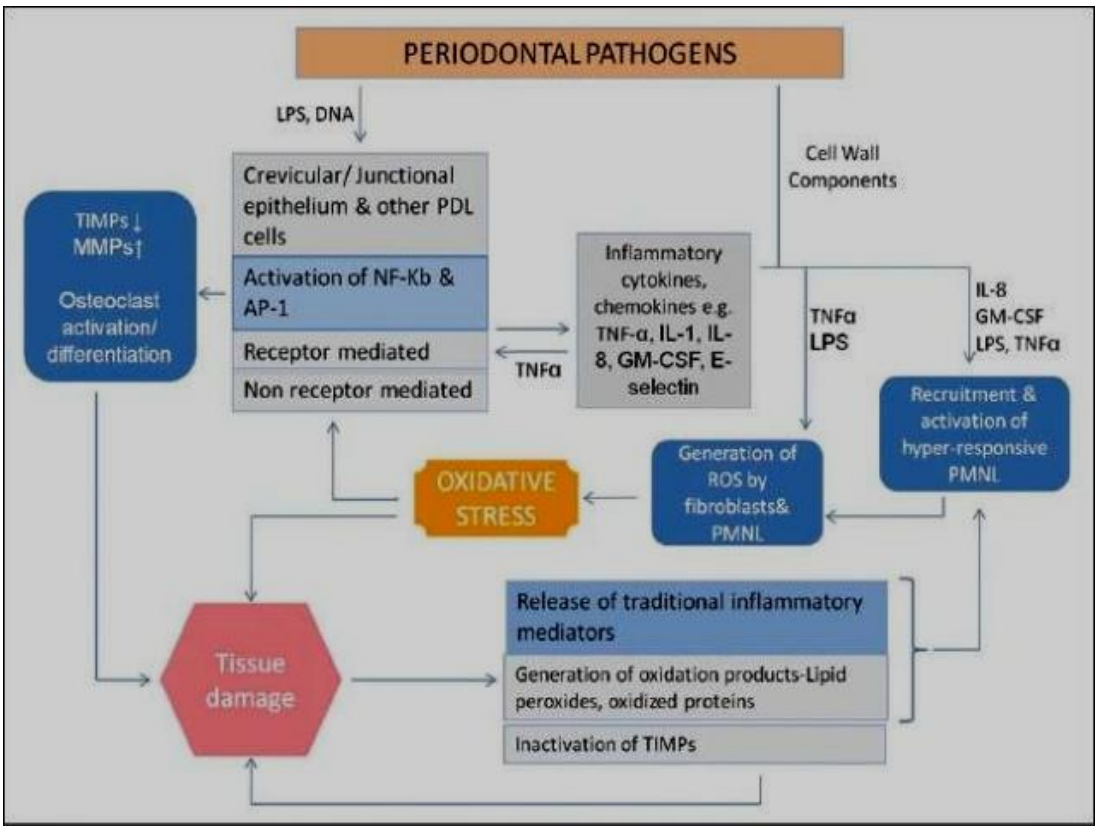
| Periodontitis is induced in susceptible hosts by a polymicrobial community, in which different members have distinct roles that converge synergistically to cause destructive inflammation

Microbial virulence strategies of periodontal pathogens (Amona A, 2010)

Selected Bacterial Properties Involved in Evasion of Host Defense Mechanisms

Host Defense Mechanism	Bacterial Species	Bacterial Property	Biologic Effect
Specific antibody	*P. gingivalis* *P intermedia* *P. melaninogenica* *Capnocytophaga sp.*	IgA and IgG degrading proteases	Degradation of specific antibody
Polymorphonuclear leukocytes	*A. actinomycetemcomitons*	Leukotoxin	Inhibition of PNM function
	F. nucleatum	Heat-sensitive surface protein	Apoptosis (programmed cell death) of PMN
	P. gingivalis	Capsule	Inhibition of phagocytosis
	P. gingivalis *T. denticola*	Inhibition of superoxide production	Decreased bacterial killing
Lymphocytes	*A. actinomycetemcomitans*	Leukotoxin	Killing of mature B and T cells; nonlethal suppression of activity
	A. actinomycetemcomitans	Cytolethal distending toxin	Impairment of function by arresting of lymphocyte cell cycle
	F. nucleatum	Heat-sensitive surface protein	Apoptosis of mononuclear cells
	e. *forsythus*	Cytotoxin	Apoptosis of lymphocytes
	P. intermedia *T. denticola* *A. actinomycetemcomitans*	Suppression	Decreased response to antigens and mitogens
Release of IL-8	*P. gingivalis*	Inhibition of IL-8 production by epithelial cells	Impairment of PMN response to bacteria

III. Innate Immune Responses To Periodontal Infection



- **The bacterial challenge induces changes in the epithelium to facilitate both vascular permeability and the influx of neutrophils**

Junctional epithelium is the structure initially most directly challenged by bacteria.The cells express intercellular attachment molecule and leukocyte function antigen 3 on their surfaces even under healthy noninflammatory conditions **(Crawford JM,1992)**and intercellular attachment molecule **1** expression by keratinocytes can be upregulated by pro-inflammatory cytokines but not by lipopolysaccharide **(Tonetti MS 1996)**

- **The bacterial products and epithelially derived cytokines also activate the local tissue mononuclear cells that shape the local immune response**

Soon after inflammation starts, however, the exudatefrom the vessels becomes predominated bymononuclear cells. In addition to endothelial cell adhesion molecule 1, activated endothelial cells express vascular cell adhesion molecule 1, which selectively binds mononuclear cells, allowing them to exit the small blood vessels and become a part of the extravascular exudate. Very soon after the initiation of the acute inflammatory response, small lymphocytes consisting of both T cells and B cells predominate in the tissue infiltrate. Subsequently, in the presence of antigen and various cytokines, these lymphoid cells begin to enlarge and replicate to form clones of CD4' and CD8+ T cells, and the B cells are driven to differentiate into clones of antibody producing plasma cells

IV. Humoral Immunity In The Periodontium(Teng Yt, 2006)

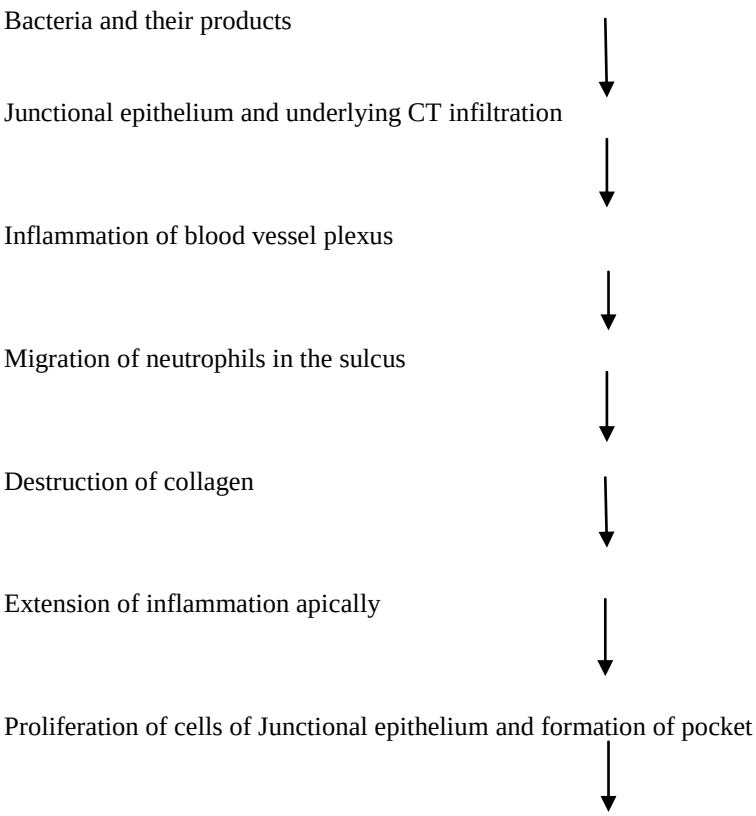
- **Future Perspective**

There have been considerable interest and efforts in generating protective or effective mAbs as potential vaccines in treating P. gingivalis infection **(Gibson et al., 2004; Kobayashi et al., 2004)** than with any other periodontal pathogens

Monoclonal Antibody or Igs Reported for Periodontal Protective Immunity

Microbial Species and Antigen Involved*	Clone (mAb)	Host Characteristics Tested	Reference/Year
P. gingivalis 381 Hemagglutinin-40 kDa	HMGD1	Higher antibacterial killing *in vitro* Inhibit hemagglutination	Kobayashi *et al.*, 200 Tagawa *et al.*, 2004
P. gingivalis A7436 Bacterial whole cells	serum IgG	Enhance bacterial clearance Induce protective immunity for alveolar bone loss in mice	Gibson *et al.*, 2004
P. gingivalis 33277 Hemoglobin	HA2	Stimulate immune protection in a rat (*via* IgG and Th2/Th1-driven response)	DeCarlo *et al.*, 2003
P. gingivalis DNA-Rgp vaccine		Protective Igs response in a mouse abscess model	Yonezawa *et al.*, 200
P. gingivalis	61BG 1.3	Selectively prevent bacterial recolonization for up to 9 months in human subjects with severe periodontitis	Booth *et al.*, 1996

However, there is presently no mAb or Igs available to study the potential effects or therapeutic efficacy associated with A. actinomycetemcomitans infection in the periodontium, although a few potential targets have been suggested (Cao et al., 2004).



V. conclusion:

Periodontitis is an infectious disease process. Bacteriaand their products interact with the junctional epithelium and penetrate into the underlying connectivetissue. The small blood vessel plexus immediatelydeep to the junctional epithelium becomesinflamed, leukocytes exit the post-capillaryvenules and there is a very large increase in thenumbers of leukocytes, especially neutrophils, migratingthrough the junctional epithelium and intothe sulcus or pocket. The collagen and other componentsof the perivascular extracellular matrix aredestroyed. As supragingival plaque extends apicallyinto the gingival sulcus, the coronal cells of the junctionalepithelium are stimulated to proliferate, and agingival pocket is formed. Later on, the apical cellsof the junctional epithelium are induced to proliferateand extend apically along the root surface, subsequentlyto be converted into an ulcerated pocket epithelium. At an early stage, there is an enlargingleukocyte infiltrate dominated by lymphocytes, includingB cells and T cells with characteristics ofboth T-helper 1 (Thl) and Th2 cells. Subsequently,the lesion becomes dominated by B cells but alsopresent are T cells, macrophages and neutrophils, allof which become activated. B and T cells are antigenicallyormitogenically activated to replicate togive rise to clones, and B cells are driven to differentiateinto clones of antibody producing plasma cells.As the disease worsens, periodontal pockets deepen,the components of the extracellular matrix of thegingiva and periodontal ligament are destroyed andalveolar bone is resorbed.

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