PATHOGENESIS OF PERIODONTAL DISEASE

Introduction

Inflammatory and immune reactions to microbial plaque are the predominant features of gingivitis and periodontitis. The inflammatory reaction is visible both clinically and microscopically in the affected periodontium. Inflammatory and immune processes operate in the gingival tissues to protect against local microbial attack and prevent microorganisms or their damaging products from spreading into or invading the tissues. These host defense reactions are, however, also considered potentially harmful to the host in that inflammation can damage surrounding cells and connective tissue structures.

Furthermore, inflammatory and immune reactions that extends deep into the connective tissue beyond the cemento-enamel junction (CEJ) may include loss of connective tissue attachment to the tooth involved as well as loss of alveolar bone. These “defensive” processes could therefore paradoxically contribute to the tissue injury observed in gingivitis and periodontitis.

Initiation of periodontal disease

The pathogenesis refers to biological and histological events that occur in the tissue during the process of conversion from the healthy state to diseased one. Most normal subjects maintaining a high standard of oral hygiene are not likely to develop advanced periodontal disease. Experimental, short-term clinical studies have shown that microorganisms quickly start to colonize clean tooth surfaces once an individual withdraws from mechanical tooth cleaning; within a few days microscopically and clinical signs of gingivitis are then apparent. These inflammatory alterations are resolved or reversed when adequate tooth-cleaning measures are resumed. The inflammatory changes may remain confined to the

gingival area for several years, but at some sites gingivitis eventually shifts to destructive periodontal disease resulting in loss of connective tissue attachment and alveolar bone. Clearly some imbalance of the host-microbial relationship is occurring in the destructive lesions, which may be unique to that site and to periodontal susceptible individuals.

Mechanisms of pathogenicity

For a periodontal pathogen to cause disease, it is essential that the pathogen be able to:-

(1) colonize the subgingival area

(2) produce factors that either directly damage the host tissue or lead to the host tissue damaging itself.

To colonize subgingival sites, a species must be able to :-

(1) attach to one or more of the available surfaces,

(2) multiply,

(3) compete successfully against other species,

(4) defend itself from host defense mechanisms.

Adhesions

To establish in a periodontal site, a species must be able to attach to one or more surfaces including the tooth, the sulcular or pocket epithelium or other bacterial species attached to these surfaces. Some of the adhesins that have been identified on subgingival species include fimbriae and cell associated proteins. Receptors on tissue surfaces that species adhere to them include proteins, glycoproteins, or polysaccharides.

Coaggregation

Many species attach directly to host surfaces, other species attach to bacteria attached to such surfaces. This phenomenon is called coaggregation, such as the coaggregation of **Lachnoanaerobaculum saburreum**, which is **non-motile** microbe, to **T. denticola**, which has the ability to migrate to the deeper periodontal tissue, the coaggregation of L. saburreum with T. denticola is characterized by **(piggyback appearance).** The whole process is highly mediated by P. gingivalis outer membrane vesicles.

Multiplication

The gingival crevice and/or periodontal pocket might be considered a rich area for microbial growth, but is in fact a rather tough environment for a bacterial species to live. The mean temperature of the area averages about **35°C** and ranges from **30°-38°C**. The pH is rather restricted **(pH 7. 0-8.5)**. Three sources of nutrient are available to subgingival organisms (diet, host and other subgingival species). Certain nutrients essential to some bacterial species must be formed by other species in that area. However, the precursors to such substances and certain specific growth factors such as hemin must be derived from the host. Gingival crevice fluid is not particularly rich in nutrients, creating a major competition for the small amounts available. In addition, nutrients delivered in relative abundance to the outer layers of plaque may not reach deeper layers.

Interbacterial relationships

Bacterial interactions play important roles in species survival. Some inter-species relationships are **favorable**, in that one species provide growth factors or facilitate attachment of another. Other relationships are **antagonistic** due to competition for nutrients and binding sites or to the production of substances which limit or

prevent growth of a second species **such as** production of **hydrogen peroxide** by **S. sanguis** which suppress the growth of **A. actinomycetemcomitans**. On the other hand, the growth of **S. sanguis** has been shown inhibited by a **bacteriocin** produced by **A. actinomycetemcomitans**.

Overcoming host defense mechanisms

Subgingival plaque microorganisms appear to overgrow and lead to severe disease in immune-compromised hosts, particularly those with neutrophil disorders. A bacterial species has a number of host-derived obstacles to overcome when colonizing a subgingival site. **These include** the flow of saliva and gingival crevice fluid and mechanical displacement by chewing and speaking. Substances in saliva and gingival crevice fluid may aid in the prevention of colonization by blocking the binding of bacterial cells to mammalian surfaces. Such factors include specific antibodies, salivary glycoproteins and mucins, which may act as non-specific blocking agents. Once a bacterial cell has successfully attached to a surface in the subgingival area, other host mechanisms come into play. **Desquamation of epithelial cells** presents a new cleansing mechanism, which is overcome by certain species by their ability to bind to underlying epithelial cells. Other species are able to invade the epithelial cells and may multiply intracellularly and spread to adjacent cells. **Specific antibody** in the subgingival area could act by preventing bacterial attachment or, in some instances, by making the bacterial cell susceptible to various phagocytic or killing mechanisms. A number of subgingival species have evolved mechanisms for evading the effect of specific antibody. Species including P. gingivalis, P. intermedia, P. melaninogenica and Capnocytophaga species have **IgG and IgA proteases** that can destroy antibody. Other species are capable of evading antibody by changing their surface antigens or possibly by mimicking the host's antigens species. A number of bacterial mechanisms exist that

might including the production of **leukotoxin** by A. actinomycetemcomitans and **capsules** by P. gingivalis and other species that inhibit phagocytosis. In addition, a number of species have developed strategies to interfere with the killing mechanisms of the polymorph nuclear leukocytes.

Virulence factors

Two general mechanisms of pathogenesis have been hypothesized. **The first** involves invasion by subgingival species. **The second** suggests a "long-range" attack where cells of the pathogenic species remain in the pocket but fragments of cells as well as other "virulence factors" enter the underlying periodontal tissues and either directly damages the tissues or cause "immune pathology"(indirectly). Virulence factors can be divided into three categories: substances that damage tissue cells (e.g. H2S), substances that cause cells to release biologically active substances (e.g. lipopolysaccharide) and substances that affect the intercellular matrix (e.g. collagenase).

Virulence factors of Aggregatibacter actinomycetemcomitans

- ☒ Leukotoxin; kills PMNs and monocytes
- ☒ Cytolethal distending toxin
- ☒ Immunosuppression factors that inhibit blastogenesis, antibody production and activate T-suppressor cells
- ☒ Inhibition of PMNs functions
- ☒ Resistant to complement-mediated killing
- ☒ Lipopolysaccharides
- ☒ Surface antigens
- ☒ Heat shock proteins
- ☒ Antimicrobial resistance

Virulence factors of P. gingivalis

- ☒ **Gingipain** is a protease secreted by Porphyromonas gingivalis. Among other functions, they work to degrade cytokines, thereby down regulating the host response in the form of reduced inflammation.
- ☒ **Capsular polysaccharide**: The capsule is a capsular polysaccharide that down regulates cytokine production especially proinflammatory cytokines IL-1β, IL-6, IL-8, and TNF-α, indicating host evasion responses.
- ☒ Fimbriae, hemagglutinins.
- ☒ Proteinases, hemolysins
- ☒ Collagenase, trypsin-like activity, fibrinolytic, keratinolytic, and other hydrolytic activities.

Red complex

The red complex is a group of bacteria that are categorized together based on their association with severe forms of periodontal disease. The red complex—among a number of other complexes were classified by Sigmund Socransky in 1998.

The three members of the red complex are:

- ☒ Porphyromonas gingivalis
- ☒ Tannerella forsythia
- ☒ Treponema denticola

Histological features of normal "clinically healthy" gingiva

Normal gingiva is **characterized clinically** by its pink color and firm consistency and the gingival margin exhibits a scalloped outline. The interdental papillae are firm, do not bleed on gentle probing and fill the space below the contact areas. The gingiva often exhibits a stippled appearance and there is a knife edge margin

between tooth and soft tissue. Normal gingiva is theoretically free from histological inflammation, but this "ideal" healthy condition has **two types**: a **super healthy or "pristine" state** which histologically has little or no inflammatory infiltrate, and the **"clinically healthy" gingiva** which looks similar clinically but histologically features an inflammatory infiltrate.

In clinically healthy gingiva features an infiltrate of inflammatory cells, predominantly neutrophils associated with the junctional epithelium and lymphocytes in the subjacent connective tissue. Exudative and transudative fluid and plasma proteins arrive in the gingival crevice region having left the vessels and travelled through the tissues to create the gingival crevicular fluid (GCF). The infiltrate at this stage may occupy as much as 5% of the connective tissue volume and is composed of monocytes, macrophages, lymphocytes and neutrophils. These cells are found in the junctional epithelium as well as in the connective tissue of clinically healthy gingiva.

Clinically healthy gingiva appears to deal with microbial challenges without progressing to a diseased state, probably because of several defensive factors which include:

1. Regular shedding of epithelial cells into the oral cavity.
2. Intact epithelial barrier.
3. Positive fluid flow of the gingival crevice which may remove non-attached microorganisms and noxious products.
4. Antimicrobial effect of antibodies.
5. Phagocytic function of neutrophils and macrophages.
6. Detrimental effect of complement on the microbiota.

Histopathological features of gingival inflammation

An experimental gingivitis study in dogs was done by **Page and Schroeder** had compared the cellular and structural composition of the affected area before and during the development of gingivitis over a **period of 28 days**. At Day 0 of this experiment the normal gingival unit has almost no inflammatory cells and is comprised of approximately 40-45% epithelium and 55-60% connective tissue. The connective tissue zone consists of collagen (60%), fibroblasts (13%), vessels (7%) and other tissue constituents, such as intercellular matrix and nerves (20%). Following plaque accumulation, neutrophils and mononuclear leukocytes readily migrate to this area and the connective tissue begins to form and increase in volume over the 28-day period. At this 28-day interval the connective tissue is comprised of lymphocytes, plasma cells and macrophages which adhere to the collagen matrix and remain in the tissue, whereas neutrophils continue to migrate into the gingival sulcus. With the extensive influx of leukocytes, a marked reduction in the amount of collagen and fibroblasts occurs and the volume of residual tissue (intercellular matrix, degraded collagen, exudates material, degenerated or dead cells) and small blood vessels increases. Page and Schroeder classified the progression of gingival and periodontal inflammation on the basis of clinical and histopathological evidence into four phases: initial, early, established and advanced stages or lesions.

The initial lesion (clinically healthy gingiva)

Inflammation quickly develops as plaque is deposited on the tooth. Within 24 hours marked changes are evident in the microvascular plexus beneath the junctional epithelium as more blood is brought to the area. Dilation of the arterioles, capillaries and venules of the dentogingival plexus is evident histopathologically. Hydrostatic pressure within the microcirculation increases and

intercellular gaps form between adjacent capillary endothelial cells. As the lesion enlarges, and gingival crevicular fluid flow increases, noxious substances from microbes will be diluted both in the tissue and the crevice. Bacteria and their products may thus be flushed from the sulcus. Plasma proteins escaping from the microcirculation include defensive proteins such as antibodies, complement and protease inhibitors and other macromolecules with numerous functions, probably within 2-4 days of plaque build-up the cellular response is well established and is helped by chemotactic substances originating from the plaque microbiota as well as from host cells and secretions. PMNs move through the connective tissue and the majority seem to accumulate in the junctional epithelium and gingival sulcus region.

The early lesion (early gingivitis)

The early lesion was develop after about **1 week** of continued plaque accumulation and **corresponds to** the **early clinical signs of gingivitis**. The gingiva are **erythematous** in appearance as a result of the proliferation of capillaries, and continued vasodilation. Increasing vascular permeability leads to increased GCF flow, and transmigrating neutrophils **increase** significantly in number.

The **predominant infiltrating cell types** are neutrophils and lymphocytes (T cell),and the neutrophils migrate through the tissues to the sulcus and phagocytose bacteria. **Fibroblasts degenerate**, primarily by apoptosis (programmed cell death), which increases the space available for infiltrating leukocytes. **Collagen destruction** occurs, which results in collagen reduction in the areas apical and lateral to the junctional and sulcular epithelium. The basal cells of these epithelial structures begin to proliferate to maintain an intact barrier against the bacteria and their products, and the epithelium can then be seen proliferating into the collagen-depleted areas of the connective tissues . Because of the **edema** of the gingival

tissues, the gingiva may appear slightly **swollen**, and, therefore, the gingival sulcus becomes slightly **deeper**. The early gingival lesion may persist indefinitely, or it may progress further.

The established lesion (established gingivitis)

The established lesion roughly corresponds to as "chronic gingivitis." The progression from the early lesion to the established lesion **depends on** many factors, **including** the plaque challenge (the composition and quantity of the biofilm), host susceptibility factors, and risk factors (both local and systemic).

In the initial work by Page and Schroeder, the established lesion was defined as being **dominated by plasma cells**, and a significant inflammatory cell infiltrate in established gingivitis occupies a considerable volume of the inflamed connective tissues. Large numbers of infiltrating cells can be identified adjacent and lateral to the junctional and sulcular epithelium, around blood vessels, and between collagen fiber bundles. Collagen depletion continues, with further proliferation of the epithelium into the connective tissue spaces. Neutrophils accumulate in the tissues and release their lysosomal contents extracellularly (in an attempt to kill bacteria that are not phagocytosed), thereby resulting in further tissue destruction. Neutrophils are also a major source of matrix metalloproteinase-8 (MMP-8; neutrophil collagenase) and MMP-9 (gelatinase B), and these enzymes are produced in large quantities in the inflamed gingival tissues as the neutrophils migrate through the densely packed collagen fiber bundles to enter the sulcus. The junctional epithelium and sulcular epithelium form a pocket epithelium that is not firmly attached to the tooth surface, that contains large numbers of neutrophils, and that is more permeable to the passage of substances into or out of the underlying connective tissue. The pocket epithelium may be ulcerated and less able to resist the passage of the periodontal probe, so bleeding on probing is a common feature

of chronic gingivitis. It is important to remember that these inflammatory changes are still **completely reversible** if effective plaque control is reinstituted.

The advanced lesion (periodontitis)

The advanced lesion, as described by Page and Schroeder, **marks the transition from gingivitis to periodontitis**. This transition is determined by many factors, which includes the bacterial challenge (both the composition and the quantity of the biofilm), the host inflammatory response, and susceptibility factors, including environmental and genetic risk factors. Histologic examination reveals continued evidence of collagen destruction that extends into the periodontal ligament and the alveolar bone. Neutrophils predominate in the pocket epithelium and the periodontal pocket, and plasma cells dominate in the connective tissues. The junctional epithelium migrates apically along the root surface into the collagen-depleted areas to maintain an intact epithelial barrier. Osteoclastic bone resorption commences, and the bone retreats from the advancing inflammatory front as a defense mechanism to the prevent spread of bacteria into the bone . As the pocket deepens, plaque bacteria proliferate apically into a niche, which is very favorable for many of the species that are regarded as periodontal pathogens. The pocket presents a protected, warm, moist, and anaerobic environment with a ready nutrient supply, and because the bacteria are effectively outside of the body (even though they are in the periodontal pocket), they are not significantly eliminated by the inflammatory response. Thus a cycle develops in which chronic inflammation and associated tissue damage continue. The tissue damage is mainly caused by the inflammatory response, yet the initiating factor—the biofilm—is not eliminated. The destruction of collagen fibers in the periodontal ligament continues, bone resorption progresses, the junctional epithelium migrates apically to maintain an intact barrier, and as a result, the pocket deepens fractionally. This makes it even

more difficult to remove the bacteria and to disrupt the biofilm through oral hygiene techniques, and thus the cycle is perpetuated.

So the **final stage** in this process is known as the advanced lesion. As the pocket deepens, probably due to the epithelium spreading apically in response to plaque irritation, plaque continues its apical down growth and flourishes in this anaerobic ecological niche. The lesion is no longer localized to the gingival, and the inflammatory cell infiltrate extends laterally and apically into the connective tissue of the true attachment apparatus. The advanced lesion has all the characteristics of the established lesion but differs importantly in that alveolar bone loss occurs, fiber damage is extensive, the junctional epithelium migrates apically from the cemento-enamel junction, and there are widespread manifestations of inflammatory and immunopathological tissue damage. It is generally accepted that plasma cells are the dominant cell type in the advanced lesion.