Periodontal Inflammation: Simplified

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Inflammation has been studied since ancient times. It was observed that as a result of irritation, injury or infection, tissues throughout the body react by increased redness (rubor), swelling (tumor), heat (calor), and pain (dolor).

Today, we know that inflammation is a process driven by cells responding to signals from the body to fend off what it perceives as an intrusion. This leads to the accumulation of fluid and leukocytes in the extravascular tissues.

The inflammatory response is a beneficial process. In the healthy periodontium, bacteria in the crevicular fluid enter the bloodstream and elicit a protective response during chewing, tooth brushing etc. The inflammatory response occurs routinely to counteract microbial challenges and eliminate them, without our awareness. We become aware of inflammation only when the response is prolonged and not successful in resolving the microbial challenge. Chronic inflammation is a destructive process that occurs when the response is not able to complete its normal cycle of removing bacteria and restoring the situation to health. The process continues for an extended period of time while the body continues trying to eliminate the bacteria. Tissue damage occurs due to the action of the cells involved in inflammation and their products.

Research on periodontal inflammation is extensive. The following is the story so far:

1. Periodontal inflammation is initiated by a bacterial stimulus
2. A cascade of events occurs in response to the stimulus (first innate, and then adaptive responses)
3. The innate response must be actively resolved. This requires substances called lipoxins, resolvins and protectins. Resolution is an active process to restore healthy equilibrium
4. Omega-3 fatty acids are precursors to resolvins. Therefore diet can affect the resolution of inflammation
5. Inflammation is affected by many risk factors including genetics

6. Over-expression of inflammation is a key aspect of aging that may influence and link diseases in the older individual. Inflammatory mechanisms are critical in the development and progression of the diseases of aging
7. Treatment of periodontal disease should not only reflect the bacterial stimulus, but must take into account the inflammatory component of the disease as well

This article discusses these factors and will attempt to bring simplicity and clarity to a very complex topic.

THE BACTERIAL CHALLENGE

The bacterial etiology of periodontal disease has been established for over a hundred years. Recent studies have also shown that it is not just the number of bacteria, but the specific bacterial types, that are implicated in the pathogenesis of periodontal disease. By the 1980s it was established that sites with periodontal disease contain predominantly Gram negative organisms while healthy sites are populated with Gram positive bacteria.
In the 1990s, the particular inflammatory response of the affected individual (the host) as well as the presence of certain specific bacteria, were found to be associated with active periodontal disease progression. The four major species implicated were P. gingivalis, A. actinomycetemcomitans, T. forsythensis, and T. denticola.

These pathogens are found in ecologic complexes (biofilm). An ecologic shift in the biofilm, like a change in available nutrients, can lead to the emergence of these specific microbial pathogens.

Periodontal inflammation is initiated by the products of biofilm bacteria such as lipopolysaccharide molecules (LPS are components of the cell wall of Gram-negative bacteria; they are not found in Gram-positive bacteria). This creates a cascade of reactions. In the healthy periodontium the products are eliminated, and the inflammation is resolved.

In the compromised periodontium, periopathogens like P. gingivalis suppress the innate host response by paralyzing a key step in the host defense system. This permits both P. gingivalis and the commensal (benign or beneficial) bacteria in the pocket to thrive and grow without any recognition or resistance by the host.

P. gingivalis may be present in low concentrations but it still has a profound effect on the amount and composition of the surrounding bacterial environment leading to periodontitis. For this reason P. gingivalis has been called a “keystone pathogen” — a species which supports and remodels a microbial community to promote pathogenesis. Many of the bacterial model studies have focused on P. gingivalis but the model applies to the other periopathogenic species as well.

The scenario is as follows:

In the deep, inaccessible, subgingival space of the compromised periodontium, P. gingivalis impedes the defense system of the body by blocking protective host receptors. This creates a dysbiosis between the host and plaque, interrupting the status quo and tipping the balance towards inflammatory disease.

Just a very small level of P. gingivalis leads to increased numbers of normally benign bacteria. This encourages a greater inflammatory response and tissue break down. The breakdown products, such as collagen fragments, flood the crevicular fluid and are a great source of nutrition for P. gingivalis and other periopathogens that require essential amino acids as a food source. (Caries pathogens thrive on sugars).

In this way “keystone pathogens” manipulate their environment (the periodontium) and their normally docile neighbours into creating a very comfortable environment and “food fest” for their own benefit.

Bacteria and the host both contribute to disease and the affected periodontal sites contain a unique microbial composition not seen in health.

Changes in the composition of gut microbiota have also been implicated in the pathogenesis of other inflammatory diseases such as inflammatory bowel disease, colon cancer, obesity, diabetes and coronary heart disease. Future treatment and prevention of these diseases may involve the identification and targeting of “keystone pathogens”.

The reaction to infection or any other noxious stimulus in the body precipitates two distinct and interconnected reactions: the innate, and the adaptive.

The innate response is an evolutionary defense mechanism that provides immediate protection. Phagocytic (ingesting) cells like neutrophils, monocytes and macrophages identify and eliminate foreign substances. These immune cells also release chemical mediators called cytokines (cyto=cell, kine=movers) that assist antibodies in clearing pathogens or marking them for destruction by other cells. The innate response is non-specific.

The adaptive response is specific. Pathogens are recognized so that a stronger response will occur should these pathogens return in the future. The adaptive response is tailored to remove specific pathogens and to remember the pathogen’s antigen signature. T cells recognize foreign antigens and specifically target them. B cells produce antibodies against the antigen. They assist the phagocytic cells in mounting a response to the noxious stimulus.

In the healthy periodontium the innate response eliminates or neutralizes foreign bodies and is protective against injury or infection. The sequence is as follows:

1. There is vascular dilation, enhanced permeability of capillaries, and increased blood flow
2. Neutrophils (also known as polymorphonuclear leukocytes or PMNs) are dispatched to the site
3. Macrophages etc are recruited to the site
4. Cell mediators (cytokines) are
produced by these recruited immune cells and by local cells in the area like fibroblasts and osteoblasts. Cytokines are the mechanism the body uses for cell communication. They are biologically active proteins that alter the function of the cell that releases it or the function of adjacent cells. They can act locally to regulate the inflammatory process or can be dispatched to distant sites.

5. Chemokines (cytokines with chemotactic properties) are released and play an important role in further leukocyte recruitment.

6. These cytokines work with the body to defend it from attack. The immune cells and their secreted chemicals attempt to destroy, dilute or wall off the injurious agent. T and B cells mediate the adaptive response.

It is noteworthy that while oral bacteria live close to a highly vascularized periodontium, very few bacteria cause systemic infections in the healthy individual. This is the result of the highly efficient innate host defense system that monitors bacterial growth and prevents bacterial intrusion into the local tissues. Dynamic equilibrium (homeostasis) exists between the dental plaque bacteria and the innate host defense system.

This is the situation as it occurs in health. When there is compromise in the health of the individual, systemically or locally, all bets are off and the process of inflammatory disease begins.

RESOLUTION OF THE INFLAMMATORY RESPONSE

Complete resolution of an acute inflammatory response and the body’s return to homeostasis is necessary for health. The leukocytes and invading bacteria must be removed without leav-
Lipoxins:
At the end of healthy inflammation, neutrophils stop secreting pro-inflammatory cytokines and begin synthesizing compounds that halt inflammation. These compounds are called lipoxins.

The resolution of inflammation and return to homeostasis is an actively regulated process, not a passive one.

They are derived from lipids (arachidonic acid—a fatty acid found in cell membranes) released from neutrophils and other inflammatory cells.

During acute inflammation, arachidonic acid is converted to proinflammatory mediators including prostaglandin. In the healthy individual, the elevated prostaglandin level signals the need to resolve inflammation. This triggers a switch in the action of arachidonic acid to now produce lipoxins, that actively halt inflammation. Lipoxins are essentially a “braking signal” for neutrophils. Aspirin transforms lipoxin into a more bioactive form with more powerful proresolving properties.

Resolvins:
Resolvins are substances that are derived from omega-3 dietary fatty acids (EPA and DHA). Several clinical studies have shown that diets rich in omega-3s are useful in the prevention and treatment of arthritis, CVD (cardiovascular disease) and other inflammatory conditions. Resolvins formed from omega-3s may be responsible for this.

Resolvins act locally to stop neutrophil recruitment and infiltration. Neutrophils are present in inflamed or injured tissue and their effective elimination is a prerequisite for complete resolution of the inflammatory response and return to homeostasis.

Results from P. gingivalis induced periodontitis animal studies showed topical resolin treatment stopped the progression of periodontal disease.

Silk threads were tied around rabbit teeth to trap bacteria and then P. gingivalis was added to induce periodontitis. One group received topical application of resolin, the other group received a placebo. The rabbits receiving topical resolin were healthy; the placebo group had periodontal disease.

Topical resolin treatment stopped the progression of disease and there was complete resolution of periodontal inflammation. Treatment resulted in bone regrowth to pre-disease levels. Histologic evidence showed both new collagen and new bone deposition.

The primary etiologic basis for periodontal disease is bacterial. However the excessive host inflammatory response and/or inadequate resolution of inflammation is critical to the pathogenesis of periodontitis. Periodontal disease results from the body’s failure to turn off its inflammatory response to infection. The result is chronic maladaptive inflammation.

As discussed, “keystone pathogens” such as P. gingivalis create a dysbiosis between the host and dental plaque. An essential step in the innate mechanism is impaired, leading to growth in the number of commensal bacteria and increased inflammation. This produces an environment that exudes a rich source of nutrients such as degraded host proteins that are just what P. gingivalis needs for survival and growth. P. gingivalis continues to exploit the environmental change, leading to more bacteria, even higher inflammation and bone resorption and a perfect niche space (deeper periodontal pockets) where everything can continue undisturbed.

Chronic periodontitis has multiple etiologies. The persistent bacterial infection of P. gingivalis is just one of these. Inflammatory disease represents a disruption of tissue homeostasis. Any factor (whether microbial or host based) that can destabilize the homeostatic equilibrium can tip the balance toward inflammatory disease. Acute inflammation that
is resolved within a reasonable time frame prevents tissue injury. Inadequate resolution and failure to return to homeostasis result in chronic inflammation and tissue destruction.\(^{18}\)

In chronic unresolved inflammation:

1. Cellular and molecular responses to bacterial challenges involve constant adjustment and regulatory feedback\(^{21}\).
2. Neutrophils, macrophages, and monocytes continue to secrete cytokines. This creates a complex chronic lesion that destroys the periodontium.
3. Cytokines promote the release of MMPs—matrix metalloproteinases (These are proteolytic enzymes implicated in normal bone remodeling. They include collagenases. Virtually all collagenases found in periodontal disease are derived from host cells not bacteria.\(^{21}\) They are also the key mediators in irreversible tissue destruction in periodontitis and have been used as biomarkers of disease progression\(^{22}\)).
4. Tissue destruction is not unidirectional. It is constantly being adjusted by host–bacterial interactions\(^{21}\).
5. Alveolar bone destruction is the result of the uncoupling of the normally tightly coupled processes of bone resorption and formation\(^{21}\).
6. Prostaglandin production plays a role in alveolar bone resorption.

Cytokines are an intermediate mechanism between bacterial stimulation and tissue destruction. They were historically identified as leukocyte products, but many are also produced by other cell types such as fibroblasts, osteoblasts, etc.\(^{23}\)

The balance between stimulatory and inhibitory cytokines, and the regulation and signaling of their receptors, may determine the level of periodontal tissue loss.\(^{23}\)

The host response is the major contributing factor for chronic maladaptive periodontal disease. A deficient host response initiates the chronic condition and a too vigorous response leads to further tissue breakdown.\(^{23}\)

**RISK FACTORS FOR PERIODONTAL DISEASE**

Clinical observation shows remarkable variations in host responses between individuals, and in their presentation of periodontal disease. Though microbial challenge is a primary initiating factor, there are many other variables that modify disease expression. These risk factors interfere with the way the body responds...
to bacterial invasion. Without the risk factors, the host may be capable of limiting periodontal tissue destruction. Disease modifiers such as smoking in the presence of bacterial accumulation may shift the immune response beyond normal parameters.\textsuperscript{24}

Bacteria initiate periodontitis. They are essential but they are insufficient. What is required is a susceptible host. Risk factors determine disease susceptibility, onset, progression, severity and outcome.\textsuperscript{21}

Through the 1990s studies were undertaken to establish specific risk factors for periodontal disease. Clinical presentation, expected progression and responses to therapy were found to be “a net integration of the host response modified by patient genetics and environmental factors”. These factors may shift the balance to more severe periodontal destruction.\textsuperscript{24}

The various environmental, acquired and inherited risk factors were found to be: diabetes, smoking, poor oral hygiene, specific microflora, stress, race and gender.\textsuperscript{25}

Diabetes increases risk through an amplified inflammatory response and depressed wound healing.\textsuperscript{26} Diabetics have cytokines that respond to the bacterial challenge at a higher rate than normal. Gingival tissues and crevicular fluid contain elevated concentrations of these cytokines, producing high levels of MMPs that promote tissue destruction and disease severity.\textsuperscript{21}

**Environment:** Smoking contributes to increased severity by the release of toxins into the oral cavity. It is the identified environmental risk most strongly associated with periodontal disease. In some studies the impact of smoking outweighs the effect of pathogenic bacteria as a determinant of outcome.\textsuperscript{27}

**Genetics:** Twin studies of adult periodontitis show greater concordance for periodontitis susceptibility between monozygotic twins than between dizygotic twins. It has been estimated that heredity accounts for about 50 percent of the enhanced risk for severe periodontitis.\textsuperscript{21}

Given the critical role of neutrophils in inflammation, genetic defects in neutrophil function would be expected to affect periodontal disease. This is the case. Genetic abnormalities in neutrophil function have been demonstrated in 75 percent of patients with juvenile periodontitis.\textsuperscript{21}

**Epigenetics:** The control of how certain genes are expressed in specific tissues can change throughout life by such factors as diet, stress, smoking and bacterial accumulation.\textsuperscript{28} This is called epigenetics.

Epigenetic alterations in DNA result in long-lasting changes in the expression of selected genes.\textsuperscript{24} Rather than involving the variability of the genetic sequence itself, epigenetic regulation is a reversible modification in gene expression determined by environmental exposures. And it may be inheritable.\textsuperscript{29}

The exposure actually changes the DNA through methylation of genetic sequences. The differential methylation of genes may contribute to the diseased state. The changes that persist in the tissue increase the susceptibility to reinfection. In this way a previous bout of periodontal inflammation may increase susceptibility to subsequent bouts of infection.\textsuperscript{30}

Of course there are also anatomic changes that result from periodontal disease, like residual pockets and bony defects. These may also predispose the individual to further periodontal infection.\textsuperscript{31}

**INFLAMMATION AS A FACTOR IN DISEASES OF AGING: THE LOCAL—SYSTEMIC LINK**

Chronic diseases such as rheumatoid arthritis, CVD, diabetes and periodontal disease may develop because of unrestrained inflammatory responses that have maladapted over decades.\textsuperscript{1,12} In inflammatory diseases, the innate and adaptive responses become unresolved and chronic. The tissues do not return to homeostasis.\textsuperscript{1}

Chronic inflammation is characterized by the continued production of cytokines, arachidonic acid derived modulators (such as prostaglandin) and many other products. Periodontitis, located in the oral cavity and thus easily observable, has been used as a model for other inflammatory diseases. Periodontitis is also unique among the inflammatory diseases because the etiology is well known (bacterial plaque) and the pathogenesis is so well characterized.\textsuperscript{20}
The periodontitis/systemic disease relationship has been studied extensively. There is substantial epidemiological evidence to suggest that periodontal inflammation can influence the course of systemic disease, especially CVD, diabetes and low birth-weight infants.\textsuperscript{20} Epidemiological studies (indirect evidence) have demonstrated statistical associations between poor oral health and several systemic diseases.\textsuperscript{32} This epidemiological evidence continues to grow.

More direct evidence through experimental studies suggest that the local inflammatory burden presented by periodontal infection causes an increased systemic inflammatory burden i.e. local inflammation can be a modifier of systemic inflammation.\textsuperscript{20}

Studies monitoring CRP (C-reactive protein) levels have shown this connection. CRP is:

1. One of the most reported biomarkers of systemic inflammation.
2. A protein whose production is triggered by infections, trauma, necrosis and malignancy and also linked to heart disease and diabetes.\textsuperscript{6}
3. Synthesized in the liver in response to proinflammatory cytokines.
4. A component of normal serum, but an elevated serum CRP reflects an elevation in systemic inflammation. An elevated CRP level has been associated with an increased risk for CVD\textsuperscript{20} and is also seen in periodontal disease.\textsuperscript{33} CRP produces biological actions that exacerbate the inflammatory response, and may also impact the initiation or progression of systemic diseases like atherosclerosis.\textsuperscript{34}

A study on animals with induced periodontitis (ligature with P. gingivalis for six weeks producing periodontitis) showed them to have elevated systemic CRP levels. After topical resolvin treatment, not only was the periodontal tissue returned to health but the systemic level of CRP was returned to that associated with health. The resolvin treatment lowers the inflammatory burden locally which results in a lower systemic burden.\textsuperscript{20}

Another study using the same model of animals with periodontitis, showed these animals to have more atherosclerosis (measured by fatty plaque deposits in their major blood vessels) than the control subjects.\textsuperscript{17} “Inflammation-resistant” subjects (with high lipoxin levels in their blood) not only failed to develop periodontal disease but their arteries were almost completely free of plaque compared to the control subjects.\textsuperscript{17}

Local inflammation from the periodontium may influence systemic inflammation through several distinct pathways.\textsuperscript{35,36}

1. Local inflammation produces micro-ulcerations through the pocket epithelium, promoting risks for distant site infections and transient bacteremia.
2. There is systemic dissemination of locally produced inflam-
matory mediators (cytokines). These then begin to act systemically, affecting other organ systems.

3. Bacterial diffusion releases a variety of biologically active molecules such as lipopolysaccharides (from the bacterial cell membrane), endotoxins, chemotactic peptides, proteins, and others that may enter the systemic circulation. These products trigger the host inflammatory response in areas far from the periodontium and elevate serum concentrations of cytokines.

4. The circulating cytokines produced by these responses affect arteries and organs.

5. CRP is synthesized in the liver in response to these circulating proinflammatory cytokines in the acute phase of inflammation. CRP can produce injurious effects on other organs, leading to vascular damage, CVD and strokes.

The bottom line is that unresolved chronic local inflammation creates a toxic systemic situation. Bacteria, proinflammatory mediators, and CRP cause damage at the local level and the dissemination of these noxious substances causes damage throughout the body.

The “oral/systemic link” is an artificial construct. The periodontal/systemic link is simply a local/systemic inflammation link. The periodontium is an integral part of the body’s systemic ecosystem. It is obvious that the local effect on one part of this ecosystem will impact the entire organism.

**THE IMPACT ON PATIENT CARE**

Understanding inflammatory response mechanisms is essential in developing innovative treatments for periodontal inflammation. While scaling and root planing is the gold standard in non-surgical therapy for chronic periodontitis, it only addresses the bacterial etiology of the disease, not its inflammatory progression. Much of periodontal disease is the result of the host response breaking down the surrounding structures.

The dynamic events of pathogenesis are determined primarily by the signaling and regulating molecules that direct cell function – the cytokines. Chronic inflammation supports the growth of pathogenic bacteria through the production of tissue breakdown products. Resolution of inflammation effectively eliminates the pathogen from the lesion by removing its food source.

Advances in treatment must address the specific bacteriological factors, the host response and the systemic progression of disease.

When we are faced with new techniques and products designed to promote periodontal health, we should be open to innovation but also judicious in our assessment. This is only possible if we are armed with a thorough knowledge of the mechanisms of periodontal inflammation and their sequelae. This knowledge arms us with the tools to provide our patients with the best clinical outcome possible.

Oral Health welcomes this original article.

References are available in our digital edition at www.oralhealthgroup.com