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HEAT SHOCK PROTEIN (HSP60) IN PERIODONTAL DISEASE: A REVIEW

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ABSTRACT

Heat shock proteins are stress proteins that are produced by cells in response to environmental stress. They have various roles in the physiological as well as pathological processes of the body. These proteins have often been implicated in the pathogenesis of various diseases. This review discusses the role of heat shock proteins (Hsp 60) in the pathogenesis as well as treatment of periodontal disease.

Key Words: Heat shock protein, Periodontal disease, Immune response

INTRODUCTION

Periodontitis is defined as “an inflammatory disease of the supporting tissues of the teeth caused by specific microorganisms or groups of specific microorganisms, resulting in progressive destruction of the periodontal ligament and alveolar bone with pocket formation, recession, or both.”¹

When exposed to a large array of environmental stresses like temperature, pH, redox potential, prokaryotic and eukaryotic cells respond by inducing the synthesis of specific proteins known as stress proteins, or heat-shock proteins (Hsps) ² Heat shock proteins have important functions in the cell such as folding, assembly, and translocation of polypeptides across membranes and play a main role in protein repair after cell damage. ³

The human and bacterial cognates of heat shock proteins are similar, sharing more than 50% sequence homology at the amino acid level. ³ During infection, Heat shock proteins from several bacterial species are recognized by the host as immunodominant antigens.⁴Heat shock protein production by several periodontopathic micro-organisms has been extensively documented. The presence of these stress proteins has been demonstrated in tissue samples from periodontitis lesions.^{5, 6}

The sequence homology between the human Heat shock protein 60 (Hsp60) and that of the periodontopathic

bacteria like *Porphyromonas gingivalis* or *A. actinomyces-temcomitans* at an amino acid level is 49% and 52%, respectively. ⁷ Despite being highly homologous between prokaryotic and eukaryotic cells, Hsp60s are considered to be very immunogenic, and immune reactions to microbial Hsp60s may be the cause for the initiation of chronic inflammatory diseases, wherein the autoimmune response to human Hsp60 could be touted as the main factor in pathogenesis of disease.⁸

This article throws some light on Heat shock proteins (Hsp60), and their role in the etiopathogenesis of periodontitis. A deep understanding of the same has the clinical implications of helping to identify patients who are at risk for developing periodontal disease based on their inability to mount an immune response to specific Hsp or Hsp epitopes. Also, *P. gingivalis* Hsp60 could potentially be developed as a vaccine to inhibit periodontal disease induced by multiple pathogenic bacteria.

HEAT SHOCK PROTEINS

Heat shock proteins participate in vital physiological processes in the cell such as folding, assembly, and translocation of polypeptides across membranes and play a role in protein repair after cell damage.³ There is a phenomenon termed heat shock response, wherein a cell that experiences increased temperature or any other stress factor, starts producing elevated amounts of heat shock proteins by enhanced transcription. ⁹

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HISTORY

The heat shock response was discovered by Feruccio Ritossa, who observed an enlargement of special sections of *Drosophila melanogaster* chromosomes (heat shock puffs) after heat treatment of the flies.¹⁰ Ritossa subjected these flies to temperature shock induced specific gene activation; the first products of these genes was identified in 1974 and the term “heat shock protein” was adopted.¹⁰ Hsp60 was first described in *E.coli* by Hendrix in 1979 and has been termed GroEL.¹¹

CLASSIFICATION

Heat Shock Proteins are classified by their molecular weight, size, structure, and function.¹²

- sHsp - Prevent aggregation of other proteins by collecting protein “garbage”, act as dustmen of cells
- Hsp60, Hsp70 - Assistance in protein folding and refolding
- Hsp90 - Stabilize substrate proteins and maintain their active, or inactive state, prevent the aggregation of other proteins
- Hsp100 - Desaggregation of proteins

HSPS & AUTOIMMUNE RESPONSE

Three models have been proposed to link microbial infections to subsequent autoimmune reactions involving Hsps¹³. These models are based on

- a. molecular mimicry between microbial Hsps and Hsps or constitutive proteins from the host
- b. inflammation-induced exposure of cryptic cell epitopes that could be a target for immune reactions
- c. antigen persistence in infected sites leading to chronic immunological reactions².

Immune responses to bacterial Hsps may generate cross reacting immunity to self-Hsp and precipitate damaging inflammatory responses.^{8,14} Young and Elliott (1989)¹⁵ showed that through these cross-reactive epitopes, T-cells with specificity for self-Hsp can be activated during infection.

The first report of antibodies against Hsps in a human disease is that of Jarjour et al (1991)¹⁶, who suggested that the difference in the levels of anti-Hsps antibodies seen between patients with diseases compared to healthy, could be an indicator of polyclonal B cell activation.¹⁷

HSP60 & PERIODONTITIS

Periodontitis is a chronic inflammatory disease characterized by mononuclear cell infiltration into the gingival

tissues, leading to connective tissue destruction and alveolar bone resorption.⁸ Although periodontal bacteria like *Porphyromonsa Gingivalis*, and *Aggregatibacter actinomycetem comitans* are the causative agents in periodontitis, the progression of the disease and the amount of severity is known to be controlled by host immune responses.¹⁸

Pleguezuelos et al (2005)¹⁹ have hypothesized that pathogenic bacteria stimulate periodontal cells to increase Hsp60 expression that could in turn initiate macrophages, to start producing proinflammatory cytokines. Due to their high conservation among various microbial pathogens and their ability to induce very strong cellular and humoral immune responses, Hsp60s are thought to play a role as candidate antigens in periodontal disease.⁸

A significant temperature elevation up to 2°C is observed in inflamed periodontal pocket.²⁰ It is very well known that pro inflammatory cytokines are produced in periodontitis. These cytokines may cause an elevation of heat shock proteins levels in the inflamed periodontium.

Lundqvist et al. (1994)⁵ found the expression of Hsp60 to be higher in gingival epithelial cells of inflamed tissue samples from periodontitis patients compared with samples from periodontally healthy individuals.

Petit et al. (1999)²¹ suggested that the higher responsiveness to Hsp60 and Hsp70 observed in gingivitis subjects may prevent the conversion from gingivitis to periodontitis.

Tabeta et al. (2000)¹⁴ reported that gingival tissue extracts from healthy or periodontitis patients contain antibodies to the *Porphyromonas Gingivalis* GroEL protein (Heat shock protein).

Ueki et al (2002)⁷ demonstrated that Human Hsp60 is expressed abundantly in periodontitis lesions and, also stimulate tumour necrosis factor (TNF) - α production from macrophages

Yamazaki et al (2002)⁸ demonstrated that Hsp60-specific T cells accumulated in the gingival lesions of periodontitis patients but not in gingivitis patients and that the T cell clones with an identical specificity to those in peripheral blood existed in periodontitis lesions.

Choi et al (2004)²² showed that *Porphyromonas gingivalis* Hsp reactive T cell immune response might be involved in immunopathogenesis of periodontal disease. They suggested that T cells in the circulating peripheral blood may home to periodontal lesions where *Porphyromonas .gingivalis* have infiltrated potentially leading to T cell response cross reactive to mammalian Hsp of gingival fibroblasts.

Pleguezuelos et al (2005)¹⁹ stated that exogenous HSP60 is capable of initiating an inflammatory response

in oral keratinocytes by increasing the expression of pro-inflammatory cytokines

Honda et al (2006)²³ proved that Hsp60 expression was up-regulated significantly in periodontitis.

HSP60 VACCINE IN PERIODONTITIS

Heat shock protein (Hsp) can be possibly explored as a candidate for vaccination against periodontitis

Choi et al (2005)²⁶ found that *P. gingivalis* Hsp60 could potentially be developed as a vaccine against multiple periodontopathic bacteria

Lee et al (2006)²⁷ found that there was a very strong inverse relationship between post immune anti-*P. gingivalis* HSP immunoglobulin G (IgG) levels and the amount of alveolar bone loss produced by bacterial infections

DISCUSSION

Although infectious diseases, by and large have a microbial aetiology, it is now an established fact that the hosts immune response to this microbial assault can itself cause destruction to host tissues. Heat shock proteins are stress proteins, and many studies have demonstrated their increased levels in periodontal disease. They generate a strong pro inflammatory response, and further, there is also the possibility of a cross reactive immune response to mammalian Hsps, due to the strong homology between the bacterial and human Hsps. Since, other infectious diseases have been controlled in the past by administration of vaccines, Heat shock proteins could be considered as a potential candidate antigen to be used as a vaccine to control periodontal disease.

CONCLUSION

Knowledge about Hsp60 and further studies establishing their role in the etiopathogenesis of periodontal disease would aid in diagnosing and also treating periodontal disease.

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