ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 10 | October - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

KEYSTONE PATHOGENESIS HYPOTHESIS

Dental Science

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ABSTRACT

Periodontitis is a bio film induced chronic inflammatory disease in which host inflammatory response primarily inflicts irreversible changes to the periodontium various hypothesis that have been postulated after much study and research. One such is the keystone pathogen hypothesis. Keystone is a central principle which all else depends. Keystone pathogen hypothesis states that even in minimal number, organisms have shown to have cause destructive changes by altering the norma l microbiota into dysbiosis. In this hypothesis the keystone pathogen is P.gingivalis. Recent studies have revealed that there is an association between the breakdown of periodontium and host immunity with that of the keystone pathogen.

KEYWORDS

Periodontium , keystone pathogen, P.gingivalis, dysbiosis, gingipain

INTRODUCTION

Periodontitis is a bio film induced chronic inflammatory disease in which the host inflammatory response primarily inflicts irreversible damage to the periodontal tissue. It has been a long time conventional thought that the dominant microorganisms present are responsible for pathologies .The interaction between the pathogen and host immune response has been extensively studied but the majority of the interaction between the microbes and the host immunity system through which the microbes causes the pathology is not completely understood . But there are various hypothesis that have been postulated after much research and study one such hypothesis is the keystone pathogen hypothesis . [5]

This hypothesis states that even in minimal number / low abundance these said microbial pathogens have shown to have cause destructive changes by transforming a normal symbiotic microbiota into a dysbiosis one.

A potential change in the normal microbiota that leads to imbalance of influx of microbes can cause dysbiosis , this causes a change in the host-microbe interaction which may cause inflammatory disorders .In case of the oral cavity the host micro homeostasis maybe altered and can cause destruction of the healthy periodontium.

Keystone pathogens are organisms that are present in relatively low numbers but cause inflammation that are disproportionately large in contrast to their numbers, in contrary to the long term believe that organisms that are dominant in the microbiota instigate inflammation . These keystone pathogen stabilize and maintain the microbiota that is associated with the disease state .

Recent studies have revealed the association between the breakdown of the periodontium and the association of the host immunity with the keystone pathogens which causes dysbiosis.[5]

This has shown that the dysbiosis causes the destruction of the tissue , which are used up by the microbes which replicate in number causing more destruction thus continuing the cycle.

This could lead to the development of a treatment modality that is specifically targeted to these microorganisms that stabilize the dysbiosis and this in turn helps us develop better diagnostic tools in identifying the disease.[4]

PERIODONTITIS AND THE KEYSTONE PATHOGEN

Periodontitis is a biofilm induced disease that causes destruction of the tooth supporting structures. Although the biofilm plays a major role in periodontitis much of the destruction is caused due to the host mediated response . studies have revealed that there are changes in the microbial composition found in a diseased periodontium much different from a healthy periodontium . This could imply that either there are new microbes that are present in a diseased Microbia that were absent or present in minute amounts or that there was a change in the interaction of various microbes in the Microbia that lead to dysbiosis which lead to the inflammatory disease.

Until recently it was widely accepted that certain group of microorganisms were involved in causing periodontitis namely the " red complex" bacteria – *P.gingivalis ,Treponema denticola and Tannerella forsythia*. However recent advances in various approach suggest that the disease involves polymicrobial synergy and dysbiosis.

P. GINGIVALIS – THE KEYSTONE PATHOGEN

The invent of an other hypothesis has given us a conclusion that periodontal pathogens transform the normal symbiotic Microbia into a dysbiosis one , which leads to the tipping of the normal host microbial homeostasis , came after evidence that *P. gingivalis* had evolved the ability to subvert the host immunity system . Accordingly it was concluded that *P.gingivalis* can disable the innate immunity in such a way that it changes the composition of the bio film triggering a destructive change in the periodontium . This has given us the conclusion that *P.gingivalis* , a gram negative bacteria that has long been implicated in the etiogenesis of periodontitis , is in keystone pathogen . This microorganism resides in the subgingival crevices.[2]

P.gingivalis rapidly invade the gingival epithelial cells .the invasion process starts with the microorganism attaches to the β 1-intergrin receptors on the cell surface . Simultaneously the *P.gingivalis* secretes the serine phosphatase (serB) which can enter the host cell and dephosphorylate and activate the actin depolymerizing molecule , this disruption allows the organism to enter the cell and it relocates into the cytoplasm. [1]

The invaded *P.gingivalis* reprograms the cells transduction and gene expression. This results in acceleration through cell cycle and suppression of apoptosis. The arg-specific proteinase (gingipain) have exhibited C5 convertase like activity .the C5 is a protein which forms a crucial part of the complement system which is a part of the innate immunity which is responsible for the inflammatory response .It also helps in phagocytosis. This protein has an α and a β chain that is connected through an di-sulfide bond . The c5 convertase enzymes cleaves this into c5a which is formed from the α chain and has spasmogenic and chemotactic property. Gingipain exhibits c5 convertase like activity which leads to increase the number of c5a which causes these to activate the c5a receptors. The c5a receptor is

activated as part of the complement cascade and has an important role in the inflammatory and regulatory functions in addition to pathogen recognition, the complement system regulates immune responses also through direct effect on the immune cells via the cross talk with the toll like receptors. Both the TLR and the complementary system are aggressively activated in response to infection and they may coordinate during antagonistic or synergistic interaction. This interaction may be exploited by the microorganism to cause destructive changes. [7]

P.gingivalis induce subversive crosstalk between c5aR and the TLR and impairs the nitric oxide dependent intracellular killing in macrophages .TLR is activated simultaneously by certain surface ligands present on *P.gingivalis* thus leading to impaired leucocyte killing. Thus *P.gingivalis* ultimately doesn't rely on immunological methods for activation of c5aR and TLR but has extra cellular cysteine proteinases that act as c5 convertase like enzymes.

The activation of c5aR has also been shown to downregulate the production of IL-12 by TLR . The IL 12 is a important cytokine in the Th1 differentiation and in cell mediated immunity the c5aR and TLR crosstalk act as a regulatory mechanism for production of IL12. , but when high level of c5a are produced this may lead to over suppression of IL12 and impair Th1 immunity. At the molecular level , the *P.gingivalis* induced c5aR and TLR crosstalk in macrophages leads to activation of cAMP dependent protein kinase for inhibition of glycogen synthase kinase 3 beta and iNOS dependent intracellular bacterial killing . By downregulating IL12 it inhibits cell mediated immunity against the bacteria.

By expressing a atypical lipopolysaccharide ,It may also prevent the activation of TLR4 dependent anti-microbial pathway in leucocytes.it also delays the recruitment of neutrophils by delaying the production of IL8 by the epithelial cells , this is crucial because the production of IL8 by junctional epithelium for the recruitment of neutrophils is an important feature of a healthy periodontium . Due to the subversion of the leucocytes there is unchecked growth of the bacteria present , this leads to increased compliment system dependent destruction which produces a lot of tissue break down products which serve as nutrition for the bacteria . This causes further shift of the periodontium into a diseased state . Those species that cannot utilize these by products of inflammation and those that cannot withstand the host mediated immunity will perish leaving the proteolytic bacteria to flourish . [6]

DISCUSSION

Study done on rodents support the hypothesis , where *P.gingivalis* even in minimal colonization levels (<0.01% of total bacterial count) caused periodontitis and considerable alternation in the organization of the oral commensal bacteria . The colonization of *P. gingivalis* was found along with alteration in the bacterial commensals and was found before the inflammatory destruction of the periodontium . The voluntary participation of the commensals was demonstrated after *P. gingivalis* colonies by itself failed to instigate a inflammatory destruction and periodontitis even when they were present in germ free mice with no commensals . The virulence of *P.gingivalis* is associated with its ability to manipulate the host response rather than by itself causing inflammation , specifically by subverting the innate immunity by involving with the complementary system and toll like receptor.

Studies done with rabbits also have shown that with colonization with *P.gingivalis* causes a shift to growth of microbes which do not require oxygen for their growth and also causes an increase in bacterial count Experiments done in non human primates with gingipain based vaccine has shown an decrease in bacterial load sub gingivally and also bone loss protection .

CONCLUSION

The keystone hypothesis has given us a new approach to characterize the human microbiome although we are very far away from understanding the complex host microbe interactions . The interesting thing to note is that why isn't *P.gingivalis* even though present in small quantities doesn't always lead to an inflammatory response this can maybe be attributed to the virulence of certain organisms and also the host immune factors which can resist the conversion of the microbiota from a symbiotic state to a dysbiosis one . Thus in conclusion keystone pathogen is a bacteria that causes dysbiosis of the commensal bacterial by disrupting the homeostasis of the host. Understanding the keystone pathogen will lead to development of proper treatment and diagnostic tools for dysbiosis diseases.

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