INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH

ISSN(print): 2833-213X, ISSN(online): 2833-2148

Volume 03 Issue 07 July 2024

DOI : 10.58806/ijhmr.2024.v3i07n15

Page No. 505-509

Periodontal Pathogens and Breast Cancer: Unravelling the Biological Links

Aashiya yadav[1], C.S. Baiju[2], Kalyani Agarwal[3],Snigdha Singh[4]

[1]Intern, Sudha Rustagi College of Dental sciences and research, Faridabad, Haryana, India

[2]Professor Sudha Rustagi College of Dental sciences and research, Faridabad, Haryana, India

[3]Intern, Sudha Rustagi College of Dental sciences and research, Faridabad, Haryana, India

[4]Intern, Sudha Rustagi College of Dental sciences and research, Faridabad, Haryana ,India

ABSTRACT: Breast cancer and periodontitis, potentially related conditions affects millions worldwide . Latest research reveals that both the diseases share common pathways and these play a critical role in the development , progression and treatment of both conditions . Periodontitis , a chronic progressive inflammatory disease of the periodontium is being highlighted for its incrimination in causing various systemic diseases . The aim of this article is to put light onto all probable pathways that makes periodontal inflammation a risk factor for Breast cancer .. This article draws attention to the commonalities shared by the two diseases, in the context of chronic inflammation , microbial dysbiosis and immunological pathways in the initiation and progression of breast cancer . It emphasizes the role of multifaceted research to reveal the underlying pathways seen in this association . The inflammatory microenvironment seen in periodontitis mimics the microenvironment that brings about the process of oncogenesis in breast cancer . Crucial bacterial species intertwined in periodontitis, like Fusobacterium nucleatum and Porphyromonas gingivalis, are seen within breast cancer tissues, indicating a possible etiological link through bacteremia and later metastatic colonization . The inflammatory terrain specific of periodontitis, rich in cytokines, prostaglandins, and interleukins, simulates the inflammatory environment that promotes oncogenesis in breast tissue . Inheritable tendencies and hormonal influences, particularly estrogen metabolism intermediated by oral and gut microbiota, further intertwine these conditions . Elevated C- reactive protein situations, a marker of systemic inflammation seen in periodontitis, are also associated with increased breast cancer threat . Research indicates that elevated levels of molecules like RANK and its ligand RANKL may promote progression and metastasis in breast cancer . A comprehension of these pathways that link Periodontitis to breast cancer can offer beneficial awareness for developing preventive and curative strategies, if proven . Such knowledge could lead to innovative interventions targeting inflammatory processes potentially mitigating the risk and progress of the two diseases . After going through various available literature it could be said that periodontal pathogens might influence breast cancer either directly or through systemic inflammatory pathways . While some evidence hints at a possible link between periodontitis and breast cancer . Databases including PubMed , PubMed Central and ResearchGate were searched for articles yielding 32 relevant English articles between 2016 to 2023, which had one of the keywords of “Periodontal Disease” , “Breast cancer” , “Inflammation” and “Myeloid derived Suppressor cells” in their titles . A total of 13 English articles were selected by the researcher for final analysis.

KEYWORDS: “Periodontal Disease”, “Breast cancer” , “Inflammation” and “Myeloid derived Suppressor cells”

I. INTRODUCTION

Periodontitis is a slowly progressing infectious disease which result in inflammation within the supporting tissue of teeth, attachment loss and progressive loss of bone . Periodontitis is not only limited to area of oral cavity but is also associated with several systemic diseases like diabetes mellitus and cardio vascular diseases . There is a presumable link between periodontitis and various forms of malignancies amongst those are breast cancer and Squamous cell carcinoma . Breast cancer is the second most common malignancy affecting one in every 8 women worldwide[1] . Approximately 25% of female cancer cases in india are breast cancer and the rate of incidence was found to be 25.8 in 100,000 women[2] . The ora meta analysis of 11 studies by shao et al suggested that the risk of developing female specific BC was 1.22 times greater among patients with periodontal disease than those without periodontal disease[3]. Some common elements of concern for the development of breast cancer are chronic inflammation, genetic factors and increase estrogen levels.

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Periodontal disease is an opportunistic dysbiotic condition in which there is an imbalance between sub gingival community and host immune response . Since periodontitis is a chronic inflammation, where the inflammatory components are found to be linked with the advancement of systemic disease like breast cancer Among which the most prevalent bacteria found in periodontitis are Fusobacterium nucleatum , Tanerella forsythia , Porphyromonas gingivalis . These are found to be associated with chronic inflammation and provide susceptible condition for carcinogenesis by releasing toxins and allocating mediators like prostaglandin , cytokine and interleukins . This results in bacteremia contributing to cellular differentiation seen in oncogenesis studies suggest that proinflammatory mediators are responsible for activation of cell signalling pathways which are responsible for breast cancer . Oral microbial Fusobacterium nucleatum species were able to inhabit the lactiferous duct of breast tissue by transferring into the systemic circulation . Fusobacterium nucleatum is one of the most prominent bacteria associated with periodontitis which is gram negative anaerobic oral commensal to human oral cavity , spindle shaped non spore forming bacteria . Studies found the above mentioned bacteria to be found in cancerous human breast tissue . The crosstalk between all above mentioned proinflammatory mediators produces a perfect micro environment for accelerating breast cancer . There are few findings that suggest association of periodontitis with breast cancer . Therefore the aim of this article is to bring light to all the possible pathways bridging the two diseases . Knowing the link between two diseases can be beneficial for developing better health care strategies and preventive measures for women at higher risk of breast cancer.

II.INFLAMMATORY COMPONENTS IN BREAST CANCER

Breast tissue is made up of three layers which include glandular (lobules) tissue , connective or fibrous tissue and the adipose tissue (fatty tissue) . chronic inflammation in breast tissue initiates the involvement of certain cells eg. immune cells like CD4+ , CD8+T, macrophages, dendritic cells, Adipocyte, fibroblasts , Natural killer cells . In breast cancer, 50% of cells within tumor are tumor associated macrophages (TAM's), lymphocytes , cancer associate d adipocytes and crown like structures . TAM's express two different phenotypesM1 and M2 [4] . During early stages of cancer macrophages are exposed to Pro inflammatory cytokines IL-1beta and IL-6 and these macrophage release M1 related factors which have protumorigenic properties . In established, progressive breast cancer IL4 , IL3 cause activation of M2 related factors i.e. IL-10 and TGF-beta which are involved in immunosuppression against TAM's . cancer associated factors secrete inflammatory factors and modify the behaviour of breast cancer cells which then increa se CCL-2 , CCL-5, IL-1beta , IL-6 , TNF-alpha , leptin , initiating metastasis . Crown like structures that are formed by confluence of macrophages (M1) and adipocytes bind at CCR 2 receptors causing release of TNF-alpha ,IL-1 , IL-6, cox-2 derived PGE-2[5](as mentioned in fig 1).

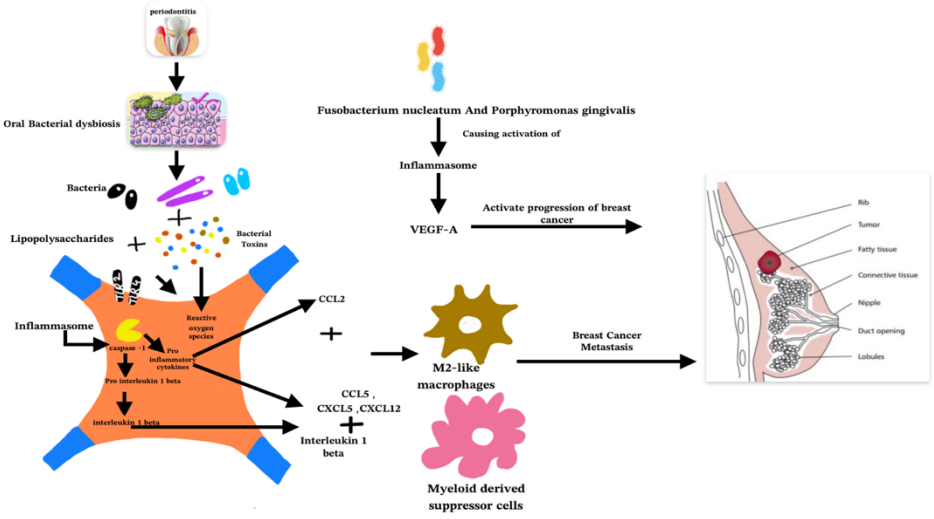

fig 1. Inflammatory components associated with breast cancer pathogenesis

III. ROLE OF INFLAMMATORY PATHWAYS LINKING PERIODONTITIS AND BREAST CANCER.

A. Influence of oral bacterial dysbiosis

periodontitis is a chronic inflammatory disease involving colonization of certain gram negative species like Porphyromon as gingivalis , Tanerella forsythia , Fusobacterium nucleatum , Actinomyces , Prevotella and few gram positive species like Streptococcus and Staphylococcus .

Parhi et al reported that Fusobacterium nucleatum invaded the breast tumor tissue and induce tumor growth and progres sion and another study suggested that the invasion of Fusobacterium nucleatum might be induced by bacteremia[6]. Fusobacterium nucleatum has been observed in cancerous human breast tissue, with stimulation of breast cancer advanc ement in murine models[7,8].

Periodontitis being a chronic inflammation shows increase in microbial load which further leads to increase in virulence factor like bacterial toxins , lipopolysaccharides (present in cell membrane of gram negative bacteria) which initiates the inflammatory pathways.

B .Role of Inflammasome signalling pathway:

Inflammasomes are complex of proteins , involved in immune response has been implicated in various disease including periodontitis and cancer .

Fusobacterium nucleatum and Porphyromonas gingivalis have the ability to develop different mechanism , Inflammasome activation and function hence it indirectly contributes to breast cancer[9].

Inflammasome mediates the expression of adipocyte mediated vascular endothelial growth factor -A (VEGF-A) and accelerates progression of breast cancer .

The Inflammasome contributes to the inflammatory micro environment by activating inflammatory signalling pathway lik e caspase -1. Pathway (causing activation of caspase -1 enzyme) and interleukin-1 signalling pathway .

Inflammasome can have both anti and pro tumorigenic effects .

Inflammasome signalling pathway is observed in inflamed gingival fibroblasts[10].

C. Role of toll like receptors:

TLR's like TLR2 and TLR4 are present on cell membrane of gingival fibroblast which participate in recognition of lip opolysaccharide by potentiating the Inflammasome signalling cascade via NF kappa beta activation , expression of pro i nflammatory cytokines and reactive oxygen species production[10] . Inflammatory cytokines like IL-1beta further promotes the release of CCL-5 , CCL-2 , CXCL-12 , and to initiate an acute immune response supporting macrophage and Myeloid derived suppressor cells and macrop hages will finally establish metastatic niche at inflammatory sites .

In the early stages of tumor progression interleukin and CCL-2 and CCL-5 recruit M2 like macrophages and myeloid derived suppressor cells (MDSC's) in head and neck lymph nodes[10](as me ntioned in figure 2.)

IV. POSSIBLE LINKS BETWEEN PERIODONTITIS AND BREAST CANCER.

A. GENETIC FACTORS

There are common target genes of periodontitis and breast cancer which belong to serpin family A member 1(SERPIN A1) and transferrin (TF) . The loss of alpha-v-beta-6 integrity function causes periodontal disease and is also related to the occurence of breast cancer[11].

B. RANK AND RANKL

Study suggests RANK and its ligand RANKL increase during periodontal disease and suggests these have a role in eac h step of initiation and progression of breast cancer hence it could be a possible link between periodontitis and breast cancer.

C. ROLE OF OESTROGEN

Oral and gastrointestinal microbes mediates steroid hormone metabolism and synthesize biologically active oestrogen mi metics that have the potential to promote development of breast cancer[12].

Abnormal function of oestrogen and its receptors affects the resorption of alveolar bone and the differentiation of perio dontal ligament stem cells , thereby affecting the process of periodontal disease .

It also participates in the occurrence and development of breast cancer due to this common factor in both the diseases there could be a possible relationship between the two diseases.

D. C Reactive protein

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Elevated levels of reactive protein are found in periodontitis, that are associated with high levels of infection with peri odontal pathogens

Dye et al, reported high serum titres to Porphyromonas gingivalis in presence of periodontal disease which are indepen dently related to high C Reactive protein [13] .

C reactive protein levels which are found to be increased in periodontal disease, is a risk factor for breast cancer and also affects the occurence and development. of cancer hence linking the two diseases

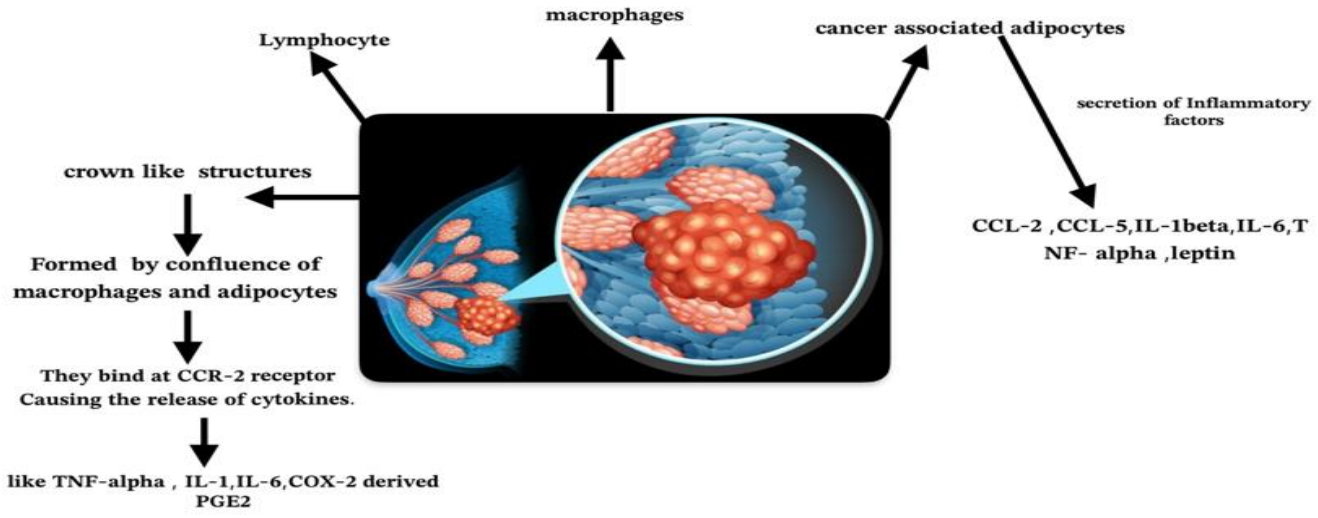

Fig 2. Represents plausible processes connecting periodontal inflammation, progression and metastasis of breast cancer. Bacteria load like lipopolysaccharide (LPS), bacterial toxins etc causing increase in virulence factors which in turn initiates inflammatory pathways.TLR-2 and TLR-4 (toll like receptors) present in gingival fibroblasts are involved in recognition of LPS and simultaneous activation of caspase-1 pathways. Pro inflammatory cytokines are releasedIL1ß,CCL2,CCL5,CXCL5,CXCL12 creating a metastatic niche by recruiting MDSC's (Myeloid derived suppressor cells), M2 macrophages.

CONCLUSION

exploration of the relationship between periodontitis and breast cancer reveals a compelling narrative woven around the role of inflammation .

Through a synthesis of existing literature , it becomes evident that chronic inflammation, a hallmark feature of periodon tal disease, may serve as a potential bridge linking these seemingly disparate conditions .

The intricate interplay between inflammatory mediators , immune responses , and tissue microenvironment offers a plaus ible explanation for the observed associations .

However, while the evidence hints at a possible connection, it is essential to tread cautiously and acknowledge the com plexities inherent in such relationships .

The pathophysiological mechanisms underpinning periodontitis associated inflammation and its impact on breast cancer d evelopment remain incompletely understood .

Thus ,further investigation is warranted to unravel the intricate web of molecular pathways and cellular interactions invo lved .

Understanding this association offers new avenues for therapeutic interventions targeting inflammation, not only to impro ve oral health but also to potentially mitigate the risk and impact of breast cancer .

Periodontal medicine as a separate entity connecting oral & systemic links might soon have Breast cancer as a point of discussion before we reach a conclusive remark in our literature .Moving forward , interdisciplinary research efforts ar e warranted to unravel the complexities of this link, paving the way for novel preventive and treatment strategies in bo th periodontal and breast health.

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