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Research Article

ORAL CANCER AND PERI IMPLANTITIS-INFLAMMATORY CARCINOGENESIS

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A B S T R A C T

Cancer research is a never ending science and shedding light in the pathogenesis and multifactorial causation of cancer is interesting and at occasions puzzling. Chronic inflammation has added a significant dimension in this regard. Biomaterial science has made rapid progression in the recent times and undoubtedly has contributed a great lot in replacement and augmentation. However surprisingly at rare occasions has been a debatable reason for carcinogenesis with chronic inflammation around the implant being the prime cause in evoking transformation of normal cells to neoplastic cells. Inflammation based carcinogenesis results from aberrations in apoptosis and phagocytosis leading to mutations, proliferation and cell damage due to presence of enriched reactive oxygen and nitrogen species leading to cancer prone environment and ultimately biomaterials beyond their benefits thus very rarely lead to inflammation induced oncogenesis.

INTRODUCTION

Research in cancer has always been a challenging science and it has been revolutionized with lateral light on the concept of inflammation induced carcinogenesis surprisingly resulting from the foreign bodies with emphasis on the biomaterial implants. According to the National Institute of Health consensus development conference, a biomaterial has been defined as any substance (other than a drug) or combination of substances, synthetic or natural in origin, which can be used for any period of time, as a whole or as a part of a system which treats, augments or replaces any tissue, organ or function of the body (Boretos and Eden, 1984).

History and Journey of Biomaterials

The history of biomaterials dates back to Egyptian mummies wherein artificial teeth, eyes, ears and noses were noticed and waxes, glues and tissues were used by Indians and Chinese as part of preconstruction and replacement of lost and damaged structures of the body. The journey of biomaterials from inception till date has taken several cross roads with wood, glue, rubber, tissues from living forms and synthetic substitutes such as iron, gold, zinc and glass used as biomaterials in the ancient days; a variety of materials such as metals which include gold, tantalum, $Ti_6 Al_4V$, 316 L stainless steel, Co- Cr alloys, titanium alloys), ceramics (alumina, zirconia, carbon, titania, bioglass, hydroxyapatite), Composite and polymers.

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Classification

Biomaterials have been classified as bioinert, bioactive and biodegradable. Bioinert refers to a material that retains its structure in the body after implantation and does not induce any immunological host reactions. Bioactive refers to materials that form direct chemical bonds with bone or even with soft tissue of a living organism. Bioresorbable refers to materials that degrade in the body while they are being replaced by regenerating natural tissue; the chemical byproducts of the degrading materials are absorbed and released via metabolic processes of the body.

Ideal characteristics and selection parameters for biomaterials

Any biomaterial should be non toxic, non carcinogenic, chemically inert, stable and mechanically strong to withstand repeated forces during lifetime. The biomaterial selection depends upon certain parameters such as host response, biocompatibility, biofunctionality, mechanical properties of biomaterials, appropriate design and manufacturability, toxicology, functional tissue structure and pathobiology, high corrosion and wear resistance, long fatigue life, modulus equivalent to that of bone and most essentially adequate strength.[1]

Journey of inflammation induced carcinogenesis

The pioneer of inflammation based carcinogenesis was Dr. Boone and his colleagues who serendipitous discovery established the relationship between inflammation and cancer with focus on reactive oxygen and nitrogen species which were involved in initiation and progression of malignancy.[2]

The history of inflammation induced carcinogenesis dates back to 1941, when Turner identified foreign body induced sarcoma in rat using a disk of Bakelite.[3] Additionally Brand *et al* studied and established that foreign body induced cancer development was associated with shape, size, smoothness, hardness, porosity, electrostatic load,[4] gender and strain of the host.[5] Interestingly Oppenheimer effect was established which revealed the fact that cancer causing material was not of degradable nature and had smooth surface.[6,7] Concave shape[8] and smooth surface with less porosity[9] of biomaterials induced more intense fibroblastic reaction and with fibroblast playing a key role in foreign body induced sarcomas such as fibrosarcomas, malignant fibrous histiocytoma, pleomorphic sarcomas, myxosarcomas, hemangiosarcomas, rhabdomyosarcomas, osteosarcomas, leimyosarcomas and mixed variety.[10] Apart from fibroblasts, macrophages have a very significant role to play in inflammation based carcinogenesis. Pericytes also contribute in that they support angiogenesis.[8] Most notably it is essential to recognize the fact that p53 gene is inactivated by inflammation related reactive oxygen and nitrogen species.[11]

Pathophysiology of inflammation based carcinogenesis

The fundamental aspect relating to inflammation induced cancer dates back to 1863, when Virchow first noted that cancer occurs at regions of chronic inflammation[12] which was further supported by several epidemiological studies.[13] As a matter of concern this fact was further explored with respect to reactiveand nitrogen species generated by inflammatory cells which were suspected to play a key role in causing mutation and leading to cancer formation.[14] Further studies proved that apart from inflammatory cells mediators such as cytokines, chemokines and few enzymes were associated with cancer development.[13]

Though inflammation is a normal physiological response to tissue damage, [15] it is imperative that inflammation is regulated by certain mechanisms so that it does not last for very extended period.[16] However when there is dysregulation in this process, the persistently activated inflammatory cell macrophage generates excessive amount of growth factors, cytokines, oxygen and nitrogen DNA damage and these mutations result in neoplastic transformation through mutagenic agents such as peroxynitrite.[17, 18]

In general the process of malignancy is associated with non compliance with anti growth signals, evading apoptosis, unco ordinated and dysregulated proliferation potential, promotion in angiogenesis and crucially metastasis.[19]

Inflammation-Mutation-Carcinogenesis

In continuum , the persisting macrophages and T lymphocytes generates tumor necrosis factor alphaand macrophage migration inhibitory factor which aggrevates DNA damage.[20] Notably the migration inhibitory factor causes impairment of p 53 dependent protective responses thus leading to accumulation in oncogenic mutations.[21] Also the migration inhibitory factor intereferes with Rb-E 2F pathway leading to tumor development.[22]

Impact of inflammatory microenvironment in Carcinogenesis

The key component in the microenvironment is the macrophage. Tumor associated macrophages play a twin role in carcinogenesis by inhibiting anti tumor mechanism and promoting tumorigenesis mechanism. This is achieved with the aid of IL-10 and Prostoglandin E2 as part of anti tumor response[23] and Vascular endothelial growth factor (VEGF), endothelin-2 and urokinase type plasminogen activator (angiogenic factors) as part of facilitating tumorigenesis.[24] In addition tumor associated macrophage also is associated with liberation of IL-1 which is connected with upregulation of VEGF transcription.[25] Most significantly invasion and metastasis is promoted by TAM with the generation of Matrix metalloproteinases (MMP - 2 and 9) which causes destruction of extra cellular matrix and basement membrane.[26]

In addition to TAM, the activated mast cells release angiogenic growth factors such as VEGF/ vascular permeability factor, basic fibroblast growth factor, angiogenic regulators such as heparin, histamine; MMP-9 and mast cell specific proteases-MCP 4 and 6 which are associated with angiogenesis, invasion and metastasis.[27-31]Neutrophils play a similar role like TAM and mast cells.[32]

Cytokines such as IL, TNF-alpha, growth factors and differentiation factors promote cell growth and differentiation and suppress apoptosis of altered cells at the inflammatory site.[33, 20, 21] Tumor derived cytokines such as Fas ligand, VEGF and transforming growth factor-beta, may stimulate the inhibition of immune response to tumors.[34] TNF is significant in inhibiting apoptosis due to the release of Nuclear factor kappa B.[15] Specifically TNF-alpha promotes angiogenesis and tumor growth by promoting a variety of angiogenic factors, thymidine phosphorylase and MMP s.[12, 35, 36, 37]

Chemokines also play a crucial role in tumor invasion and metastasis by mediating the directional migration of tumor cells to specific distal organs via circulation in a similar manner to its control of leukocyte migration[19] and facilitate metastasis by inducing expression of MMP's and collagenases degrading the basement membrane.[38-41]

The significance of nuclear factor kB (NFkB) controlled by proteins like zinc finger protein is related to the fact the proapoptic activity of anti neoplasticcyclopentenone prostaglandin involves NFkB inhibition wherein the activation of NFkB played a critical role in the suppression of p53 co ordinate apoptosis.[42, 43] Most essentially NFkB stimulates cell proliferation by inducing growth factor genes, proto-oncogene c- Myc and cell regulator cyclin D1.[44 - 46] The key mechanism in which NFkB contributes to tumorigenesis involves two fundamental principles which includes release of reactive oxygen species causing mutations inhibiting mutated pre cancerous cells from being removed.[44] Very specifically NFkB promotes pro inflammatory cytokines such as IL-6 and TNF-alpha and chemokines such as IL-8, adhesion molecules, MMP's, COX-2 and iNOS.[47] Notably the presence of adhesion molecules such as E-selectin , vascular cell adhesion molecule and intercellular adhesion molecule-1 is related to the presence of NFkBandis crucial in the micro environment of cancer.[48]

Inducible nitric oxide synthase (iNOS) an essential enzyme catalyzing NO[49]production persistently induced by pro inflammatory cytokines such as TNF-alpha, IL-1 beta and transactivation of NFkB[50] as part of inflammatory microenvironment results in tumorigenesis by upregulating angiogenesis, leukocyte adhesion and infiltration.[51]At occasions, the expression of COX-2 is found to enhance tumorigenesis in the presence of chronic inflammation.[52]

Hypoxia-inducible factor 1 alpha is a heterodimeric transcription factor[53] which may result from the activation of NFkB and COX- 2 by pro inflammatory cytokines such as TNF-alpha, IL-1 beta[54,55] and it facilitates tumorigenesis through an accentuated glycolytic activity and simultaneously causes an upregulation of VEGF in tumor development and metastasis.[56]

It is essential to consider the fact that cytokines such as IL-6 can also have an impact in activating the signal transducers and activators of transcription (STAT) through Janus activated kinases and it is a puzzling speculation that IL-6/ Janus activated kinase/ STAT 3 pathway has a complex role to play in carcinogenesis thus relating inflammatory microenvironment and cancer.[57, 58]

Evidence based odontology: Squamous cell carcinoma and dental implants

While addressing the fact relating to Squamous cell carcinoma associated with dental implants it is eesential to consider three facts which include probability of presence of pre existing (unidentified) lesions prior to insertion of implants, if the implant composition/ manipulated bone fragments served as foreign bodies in the surgical site triggering cancer, manipulation of the tissue perse invoked cancer.[59] With fascinating success of implants on one side, the complications of implants are not to be overlooked which include …..

Most common among these include post operative infection, implant fracture, periimplantitis, bone loss and failure of osseointegration with loosening of the implant.[60]With respect carcinogenesis, Periimplantitis is a common but significant complication. Clinically it can manifestsas edema, erythema, hypertrophy and occasionally as ulcerations of soft tissues. The gingival attachment in implants when subjected to inflammation may be a silent reason to evoke carcinomatous changes due to the action of cytokine mediators such as prostaglandins, interleukins 1, 6 and tumor necrosis factor along with synergistic effect of smoking, alcohol, nutritional deficiency and sometimes poor oral hygiene.[61] Implanted biomaterials have found to liberate trace amounts of residual components such as monomers, catalysts, plasticizers and anti oxidants which have been speculated to have strong co relation with inflammation induced carcinogenesis particularly sarcomatous development**.**[62]

CONCLUSION

Unravelling the association between inflammation and cancer reveals the fact that unresolved chronic inflammation[63, 64] resulting from aberrations in apoptosis and phagocytosis may lead to cell damage and proliferation due to presence of enriched reactive oxygen and nitrogen species leading to cancer prone environment.[65] Ultimately focus and research on the intriguing puzzle between inflammation and cancer necessitates unique light to shed so that preventive therapeutic approach can be undertaken in scenarios associated with inflammation induced carcinogenesis.

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