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REVIEW ARTICLE

MACROPHAGES IN HEALTH AND DISEASES: A SYSTEMIC REVIEW

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ABSTRACT:
One of the most plastic cells of the hematopoietic system that are located in almost all tissues is the macrophages. They exhibit a great deal of functional diversity. Apart of having distinctive roles in development, homeostasis, tissue repair, and immunity, they can be can be subverted by chronic insults, resulting in a causal association of macrophages with disease states. In this review, we highlight the pathophysiological role of macrophages in the normal development process and various pathologic conditions including pre-malignancies and malignant neoplasm. This pathogenesis can help in throwing light on the use of these macrophages as therapeutic targets for treatment.
Key words: Carcinoma, Lichen planus, Macrophages

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INTRODUCTION:

Role of macrophages in the non-immunological trophic cases during development have been increasingly highlighted after almost a century of its discovery by Metchnikoff. Metchnikoff first observed these cells in Ascidians where they worked as homeostatic regulators in maintaining the integrity of an organism through physiological inflammation. He contrasted this term with 'pathological inflammation' resulting from external challenges, which we now know as innate immunity.[1]

LINEAGES OF MACROPHAGES

Studies in the past literature in which emphasis was done on phagocytosis, led to the term macrophage to distinguish these cells from the polymorphonuclear microphages. The challenge for the developmental biologists is the definition of a macrophage since the time of their discovery. Two types of macrophages have been identified by the studies on phagocytosis: cells that aligned the endothelium and amoeboid cells known as histiocytes.[2, 3] Common origins of the cells has been indicated by observation of these two types of cells as they both cleared particles from the blood which evolved into the reticulo-endothelial system (RES). Since most of the cells Since, the endothelial cells and histiocytes are morphologically and functionally distinct and that because many cells can be phagocytic, name the mononuclear phagocytic system (MPS) replaced the use of the RES to classify macrophages.[3] As it became clear that some dendritic cells (DCs) can differentiate from monocytes and macrophages, the classification MPS has been refined.[4, 5] Recent identification of myeloid precursor cells which were different from endothelial cells indicated that a re-examination of the RES may be required.[5- 7] Classification of macrophages with the help of RES included bone-marrow derived precursor cells, monocytes in the peripheral blood and mature macrophages in tissues, but excluded endothelial cells and other mesenchymal cells that are not obviously derived from the bone marrow.[7]

ROLE OF MACROPHAGES IN ORAL SUB MUCOUS FIBROSIS (OSMF)

In the pathogenesis of OSMF, Macrophages have also been implicated. Increased levels of stimulated IL-1β,

TNF‑α, IL‑6, IL‑8, and a decreased level of stimulated IFN‑g have been demonstrated by Haque et al. in the peripheral blood mononuclear cells. The main sources of cytokine synthesis are the immune competent cells, especially the macrophages and lymphocytes.[8, 9] Pereira et al evaluated the role of CD68 in OSMF patients and investigated the possible correlation of macrophages in various histopathological grades of OSMF. They observed that the macrophage number was higher in the patients of intermediate and advanced stage of OSMF than that of the controls. From the results, they concluded that in the pathogenesis of OSMF, CD68 plays a vital role and therefore, can be regarded as a useful marker for assessing the progress of the disease.[10] Characterization of the inflammatory cell infiltrates in the lesional oral mucosa from OSMF patients by Haque et al by Immuno-histo chemistry (IHC). Activated T lymphocytes, especially activated helper/inducer T lymphocytes, and the macrophages were found to be the major and minor population of the cells respectively.[9] In the quantitative study of Pereira et al, a significant increase in macrophage densities in the subepithelial connective tissue of OSMF specimens was found in comparison to those in control specimens.[10] The idea of role of the cellular immune response in the pathogenesis of OSMF is suggested by the significant increase in the number of macrophages in the subepithelial connective tissue of OSMF specimens. Moreover, IL‑1β and TNF‑α have been demonstrated to upregulate mRNA expression of collagen types I and III. Intradermal injections of TNF‑α stimulate the accumulation of fibroblasts and collagen. TNF‑ α has also been shown to inhibit adherence and phagocytosis of collagen. Similarly, both IL‑6 and IL‑8 have also been implicated in the development of fibrosis. On the contrary, IFN‑g is an antifibrotic cytokine that can inhibit collagen synthesis. Improvement of keloids and hypertrophic scars by the intralesional IFN‑g treatment has been reported. Furthermore, local injections of IFN‑g reduce the contracture formation and facilitate the mouth opening in the OSMF patients.[8, 10] The presence and distribution of inflammatory cells and MHC class II antigen expression by epithelial and immunocompetent cells in OSMF patient has been investigated by Haque et al. Antibodies to T cells (CD3), T helper/inducer cells (CD4), T suppressor/ cytotoxic cells (CD8), B cells (CD20), naive T cells and monocytes (CD45RA), macrophages, Langerhans' cells (CD68), and human leukocyte antigen Human leukocyte antigen-DR (HLA‑DR)‑positive cells (HLA‑DR alpha) were used to investigate all the OSMF tissues. CD3, CD4, and HLA‑DR‑positive cells were the predominant cell population to be detected in the normal tissues. A higher numbers of CD3 and HLA‑DR‑positive cells were found in OSMF patients when compared with those of the normal tissues. Ongoing cellular immune response leading to a possible imbalance of immunoregulation and alteration in local tissue architecture is suggested by the presence of these immunocompetent cells and high ratio of CD4 to CD8 in OSMF tissues.[11] Comparison of the microvascular density (MVD) and infiltrating macrophage density (IMD) in oral OSCCs with different histological grades using antibodies such as von Willebrand factor and CD68 has been done by Bôas et al. They couldn't observe a significant correlation between MVD and IMD could not be obtained suggesting that angiogenesis does not depend on the number of macrophages present in OSCC, but their predominant phenotype.[12] El‑Rouby studied the association between tumor‑associated macrophages (TAMs) and angiogenesis in formalin‑fixed, paraffin‑embedded archival material of OSCC, and oral verrucous carcinoma. TAMs shown by IHC for CD68 and microvessels demonstrated by IHC for CD31 were quantified using an image analyzer computer system. He observed an increased TAMs density associated with angiogenesis in higher histopathological grades in oral cancer.[13]

MACROPHAGES IN ORAL LEUKOPLAKIA

Oral leukoplakia is a premalignant lesion of the oral mucosa that is characterized by a circumscribed thickening of the mucosa covered by whitish patches.[14] Although hospital-based follow-up studies have shown that between <1 % and 18 % of oral premalignant lesions will develop into oral cancer, a certain clinical subtype of leukoplakia with epithelial dysplasia has been shown to be at an increased risk for malignant transformation.[15] However, histological assessment of epithelial dysplasia has also demonstrated that not all lesions that show dysplasia will develop into oral cancer, and some will even regress.[15] Therefore, in the recent past, there has been proposal has been given regarding the development of other methods for predicting the malignant potential of premalignant lesions. In terms of the risk for malignant transformation, recent studies have

examined the molecular profiles of oral premalignant lesions. In oral premalignant lesions, genetic alterations and molecular abnormalities have been identified. In oral premalignant lesions, a loss of heterozygosity (LOH) at chromosome 9p and 3p and the absence of p19, a tumor-suppressor protein, has been frequently observed.[16,17] Although genetic alterations in epithelial cells are essential for the development of premalignant lesions, recent studies have shown that the nature of the tumor microenvironment and circumjacent stromal cells, including infiltrated immune cells, can significantly modify the outcome of these alterations. Numerous studies have demonstrated that tumor-associated macrophages (TAMs) initiate and promote tumorigenesis in many types of solid tumors, and a strong correlation between an abundance of TAMs and poor prognosis has been demonstrated in breast, prostate, cervical, and bladder cancers.[18- 21]

TAMs infiltrating colon and lung cancers have been associated with a better prognosis in patients in contrast to their tumor promoting function.[22] Analysis of the phenotypes of the infiltrated TAMs revealed that the TAMs involved in poor patient prognosis share many common features with alternatively activated macrophages or M2 macrophages, which express high levels of the scavenger receptors CD163 and CD204, high levels of the chemokines CCL17, CCL22 and CCL24, and low levels of IL-12.[19- 23] The TAMs associated with a better patient prognosis share a phenotype with classically activated macrophages or M1 macrophages, which express HLADR, inducible nitric oxide synthase (iNOS), and tumor necrosis factor-α (TNF-α), in contrast to alternatively activated macrophages. These lines of evidence indicate that the functional competence of macrophages is heterogeneous and that the functional properties are acquired and modified in response to changes in the tumor microenvironment. An increased infiltration of mononuclear cells in oral premalignant lesions and OSCC has also been reported in previous studies. [24- 28]

BONE RESORPTION

Macrophages have co-stimulatory activity on T cells and efficiently ingest particulate antigen and express MHC class II molecules. Environment can phenotypically polarize the macrophages. The classically activated macrophages (M1) are activated by IFN-γ and LPS, and alternatively activated macrophages (M2) produced in response to IL-4 or IL-13.[29] M2 macrophages have been shown to play role in resolution of inflammation with a reduced capacity to produce cytokines. In immune response and the inflammation process, cytokine and chemokine production by macrophages is a key step.[30] Cytokines interact between each other, amplify signaling, modulate cell surface receptors, and perform synergistic or antagonistic interactions on cell function. It is not only the presence of one cytokine that regulates the response, but the concentration of the same mediator can also affect the outcome of a response. Their secretion is dependent on the NF-κB in the nucleus of many immune system cells. In addition to macrophages, cytokines can be produced by both resident cells such as epithelial cells, fibroblasts and other phagocytes such as neutrophils in the periodontal tissues.[31] In disease pathogenesis, cytokines in innate response such as TNF-α, IL-1, and IL-6 are the first to start communication after microbial recognition.

Being associated and involved in osteoclastogenesis processes, IL-1β and IL-6 are the signature innate cytokines. They are produced by the macrophages and have been characteristically associated with inflammatory cell migration. TNF-α is a multi-role cytokine, that has many functions from cell migration to tissue destruction. It induces the up-regulation of adhesion molecules, stimulates the production of chemokines, and is involved in cell migration to infected and inflamed sites.[32-37] The production of other signature pro-inflammatory innate immunity cytokines, such as IL-1β and IL-6 is up-regulated by TNF-α. TNF- α is also correlated with extracellular matrix (ECM) degradation and bone resorption through its positive correlation with matrix metalloproteinases (MMPs) and RANKL expression. A significant decrease in MMPs and RANKL expression has been reported in experimental periodontitis in TNF-α p55 receptor deficient mouse. Macrophage-derived cytokines, in addition to direct actions in bone resorption, also interfere with the coupled bone formation process. [38- 40]

ORAL LICHEN PLANUS

In chronic oral inflammatory diseases such as oral lichen planus, M1 macrophages can exacerbate the condition. Oral lichen planus presents clinically as white striations, with papules or plaques, or both, that principally involve the buccal mucosa, tongue, and gingival. It is predominantly mediated by T cells and is characterized clinically as white striations, with

papules or plaques, or both, that principally involve the buccal mucosa, tongue, and gingiva. [41- 43] In the progression of the disease, the interplay between macrophages and T cells emphasises the importance of macrophages.[44] A pro-inflammatory M1 phenotype is developed by infiltrating monocytes which are recruited into the lesion because of the high levels of GM-CSF, TNF-α, and IFN-ɤ produced at the site.[44] M1 macrophages can aid progression by three main mechanisms: initiation of inflammation, activation and priming of T cells, and direct destruction of the basal membrane. They can exacerbate inflammation through the production of pro-inflammatory cytokines (TNF- α, and IL-1β), which can upregulate cell adhesion molecules on endothelial and keratinocyte surfaces and induce chemokine expression (RANTES (regulated upon activation, normal T expressed and secreted) for T cells; MCP-1 for monocytes) by oral keratinocytes, which results in increased recruitment of inflammatory cells into the lesion.[45, 46] The polarisation of T cells is influenced by the macrophages which can activate antigen-specific T cells (antigen unknown in oral lichen planus) through the secretion of differentiation cytokines (IL-12→Th1 or IL-4, IL-5→Th2).[47] T cells in the disease have been found to secrete IFN- ɤ, which is typical of Th1 subsets, and is indicative of IL-12 production by the macrophages in oral lichen planus. IFN- ɤ and IL-2 are cytokines produced by activated Th1 cells, and they function to permit the full activation of CD8+ cytotoxic T cells, which are hypothesised to kill basal keratinocytes.[48] M1 macrophages can also activated by the feedback provided by IFN- ɤ to produce TNF-alpha which can directly initiate basal keratinocyte apoptosis, and indirectly increase the rate of destruction of the basal membrane through the upregulation of MMP-9 from lesional T cells. IV collagen is cleaved by MMP-9 which causes the membrane to be destroyed and the subsequent loss of attachment of basal keratinocytes, which potentially results in keratinocyte apoptosis and further damage.[47] Destruction of the basal membrane, is causes but the macrophages which are distributed close to the damaged basal layer. There seems to be a vicious cycle of perpetuating inflammation and damage to the basal membrane, as this destruction can further initiate inflammation through the release of danger-associated molecular patterns (DAMPs).[48] Therefore M1 macrophages play a role in the progression of lichen planus by activating T cells and exacerbating inflammation at the site.[49, 50]

MALIGNANT POTENTIAL OF LICHEN PLANUS

For decades, the link between inflammation and cancer has been known. World Health Organization has defined lichen planus as a premalignant lesion although there is controversy regarding the rate of transformation.[51] M1 macrophages have the ability to aid initiation of the transformation process, and M1 cells produce reactive oxygen and nitrogen species (superoxide, hydrogen peroxide). Although this is beneficial in the short term, these reactive species have mutagenic capabilities because of their cytotoxicity to many pathogens, and in chronic inflammation (as in lichen planus) they can potentially cause the disease to progress and epithelial cells to transform.[52] Oxidation of lichen planus can take place directly by reactive oxygen species, while reactive nitrogen species can cause nitration and deamination reactions of DNA bases that lead to changes in the DNA, and increase the rate of mutation. Pro-inflammatory cytokines produced by M1 macrophages can also activate specific signal transduction pathways that can affect the expression of genes that control cellular processes such as proliferation and apoptosis.[53] a major transcription factor that is activated and acts a link between inflammation and cancer is Nuclear factor κ-B.[54] By upregulating the expression of anti-apoptotic proteins (X-linked inhibitor of apoptosis protein (XIAP), and TNFR associated factor 1 (TRAF-1), which increases cell survival), cell cycle mediators (cyclin D, which increases proliferation), and angiogenic factors (vascular endothelial growth factor (VEGF), it can promote oncogenic cell transformation thereby tipping the balance in favour of cell proliferation and survival.[55] In chronic inflammatory conditions such as lichen planus, the M1 macrophage phenotype can therefore aid the malignant transformation of cells and result in oral cancer.[56]

ORAL SQUAMOUS CELL CARCINOMA

The concept of epithelial-mesenchymal transition (EMT) was first defined by Elizabeth Hey in 1968. Reactivation of EMT could promote tumor cell migration and invasion by disruption of apical-basal polarity and loss of E-cadherin expression was discovered by later researchers. It is an essential embryonic process during which epithelial cells loose contact with their neighbours and gain mesenchymal properties, this could enable them to break through the basement membrane which separates different

tissues from the embryo.[57- 60] Tumor-associated macrophages (TAMs) are key orchestrators and a set of macrophages of the tumor microenvironment. Hence, it will greatly benefit our understanding of tumor migration and invasion that clarifying the regulation of EMT. They play major role in the connection between inflammation and cancer. In recent studies evidences have demonstrated that TAMs play major role in regulation of EMT in cancer.[61] TAMs could inhibit antitumor immune response mediated by T cell, and it promote tumor progression and also promote proliferation, invasion and metastasis of tumor cell, stimulate tumor angiogenesis.

THERAPEUTIC TARGET

In the development and progression of human cancer TAMs play critical role, it also plays a critical role in the regulation of EMT in cancer. Targeting TAMs could be a novel strategy for the treatment of human cancers. TAMs could be either tumor promoting (M2 or alternatively activated) or tumor killing (M1 or activated). Large-scale transcriptome analysis results revealled macrophages have a mixed phenotype expressing both M1 and M2 markers.[62- 64] In recent studies indicated the approach of block macrophage trophic phenotypes together with their immunosuppressive behaviors and enhance their activation, and antitumoral activities is feasible and therapeutic. The major strategy targeting TAMs for cancer therapy based upon genetic experiments is inhibition of CSF-1 signalling by anti-CSF1 receptor-neutralizing antibodies or small-molecule inhibitors.[65] TAMs are repolarised by inhibition of CSF-1R resulting in a state regulated by GM-CSF in glibastoma, cervical and breast cancer models have been demonstrated to be antitumoral.[66] Small molecule inhibitors to CSF1R could deplete some populations of TAMs and enhance tumor responses to chemotherapy by the removal of macrophage-mediated immunosuppression during the tumor recovery period. Study results showed low-dose irradiation of tumors programs macrophages to an activated state could orchestrate T cell immunotherapy. Monoclonal antibodies therapeutic efficacy of monoclonal antibodies could also be enhanced by macrophages. In mice models, monocytes and/or macrophages could be directly killed by the trabectedin could be a therapeutic agent against tumors.[67-71]

ROLE IN PROGRESSION OF DENTAL CARIES

Macrophage inflammatory protein-3α (MIP-3α), which is designated as liver and activation-regulated chemokine (LARC) and was recently listed as CCL20 in the systematic classification of chemokine ligands, is a potent chemoattractant of immature dendritic cells and T cells, and is involved in the pathogenesis of chronic inflammatory diseases such as rheumatoid arthritis, psoriasis and marginal periodontitis. CC chemokine receptor-6 (CCR6) is the only known receptor for MIP-3α. Recently, it was shown that CCR6 is expressed on memory T cells and that MIP-3 preferentially attracts these cells. In pulpitis tissue, the accumulation of a selective lymphocyte subset into inflamed dental pulp may be regulated by MIP-3 α - CCR6 interaction.[72- 73] Nakanishi et al evaluated the expression of Macrophage Inflammatory Protein 3 in Human Inflamed Dental Pulp Tissue. MIP-3 was observed in all inflamed pulp sections, and was mostly distributed in macrophages that had accumulated in the area adjacent to carious lesions. Furthermore, CCR6 expression was also observed in the infiltrating lymphocytes. In contrast, MIP-3 and CCR6 were rarely detected in normal pulp. These findings suggest that MIP-3 plays a role in the advancement of pulpal inflammation via the recruitment of CCR6-expressing lymphocytes.[74]

ROLE IN ODONTOGENIC LESIONS

The great majority of radicular cysts are lined with stratified squamous epithelium with rete pegs. It was shown that epithelial rests are residual cells, which are found in the connective tissue of periodontal ligament, which are still vital, and undergo mitosis. It has been accepted that the lining of stratified squamous epithelium of periapical granuloma or periapical cysts arises from epithelial rests of Malassez. The endotoxins can activate macrophages, resulting in the production and release of collagenase that been found in several chronic inflammatory lesions including periodontal disease. Tumour necrosis factor (TNF) is a multifunctional cytokine secreted predominantly by monocytes and macrophages. Macrophages are present in the cyst wall of the radicular cyst. Qureshi et al investigated the role of tumour necrosis factor in the pathogenesis of radicular cyst, which is by far the commonest cystic lesion of the jaws. From the results, they concluded that TNF stimulated the epithelial cell

proliferation in low concentration and inhibit the proliferation in higher concentrations.[75]

Zhong et al evaluated the presence of M2-polarized macrophages and their relationships to angiogenesis in keratocystic odontogenic tumor (KCOT). M2-polarized macrophages were detected in KCOT samples by immunohistochemistry and immunofluorescence. Meanwhile, microvessel density measured with antibody against CD31 was closely correlated with the presence of M2-polarized macrophages. In addition, macrophage colony-stimulating factor (M-CSF) significantly contributed to the activation of M2-polarized macrophages. Moreover, the results of in vitro wound healing, cell migration and tube formation assays further revealed the pro-angiogenic function of M2-polarized macrophage-like cells. This function might be associated with secretion of angiogenic cytokines, such as vascular endothelial growth factor (VEGF), transforming growth factor-β (TGF-β) and matrix metalloprotein-9 (MMP-9). This study demonstrates for the first time that M2-polarized macrophages are prevalent in KCOT, and their presence is dependent on M-CSF expression. More importantly, these tumor-supportive cells can also promote tumor angiogenesis by secreting angiogenic cytokines.[76]

ROLE IN PERIODONTAL LESIONS

Periodontal disease is an inflammatory process that affects almost 90% of the population and involves the supporting structure of teeth. It is usually a progressively destructive change leading to loss of bone and periodontal ligament around the teeth which may eventually lead to their loss. The infection starts in the gingival epithelium leading to gingivitis, and under certain conditions it will progress into the underlying connective tissue leading to periodontitis. Macrophages are important mediators of inflammation in the connective tissue infiltrate where they produce several cytokines and also present antigens to T cells.[77- 85] They are an essential part of the innate immune response to intracellular infection. They produce proinflammatory cytokines which enhance phagocytosis and in most cases result in the successful elimination of the pathogen. In addition, macrophages/monocytes are capable of differentiating to osteoclasts in response to TNF-α in the presence of RANKL. This means that these cells form a key link between the immune system and bone resorption. In periodontal disease, macrophages/monocytes are major contributors to tissue breakdown. Samples from periodontitis patients had higher numbers of macrophages/monocytes associated with greater collagen breakdown and higher level of MMPs compared to controls. Studies have shown that IL-1 was expressed predominantly by macrophages in tissue isolated from periodontal patients.[86- 88] Using an immunohistochemistry technique, Crotti et al. demonstrated that significantly higher levels of RANKL protein are associated with macrophages in the periodontitis tissues. Periodontal pathogens, such as A. actinomycetemcomitans and P. gingivalis, have been shown to activate monocytes and macrophages and stimulate the secretion of proinflammatory and tissue-destructive mediators such IL-1, TNF-α, IL-6, and PGE2. These studies demonstrate that one of the responses of macrophages to bacterial invasion of periodontal tissue is production of inflammatory mediators that contribute to the destruction of tissue components including bone.[89, 90]

VESICULOBULLOUS LESIONS

The high density of CD3+ and CD68+ cells in the bullous skin lesions as well as their perivascular location is in line with previous reports. The numerical dominance of these cells strongly suggests their critical role in the development, exacerbation and remission of these lesions. The direct association (position) between CD3+ T cells and CD68+ macrophages reflects the close interaction between them in execution of the immune response. In this respect, the presence of CD68+ macrophages is essential for uptake, processing and presentation of the antigenic epitopes associated with the major histocompatibility complex class II to the CD3+ T cells. The increased density of CD3+ cells may be due to: (1) increased antigenicity of the lesional cells; (2) production of soluble factors (chemokines); (3) increased expression of adhesion molecules; and (4) increased tissue accessibility for immune cells. Several antigens were reported in the bullous skin lesions, such as bullous pemphigoid antigen 2 (bullous pemphigoid),49 130-kDa polypeptide pemphigus vulgaris and cutaneous lymphocyte-associated antigen.40 Furudate et al compared CD163+ CD206+ M2 macrophages in the lesional skin of bullous pemphigoid and pemphigus vulgaris. They observed that the numbers of CD163+ CD206+ M2 macrophages were higher in BP than in PV. Moreover, pSTAT6+ cells, CCL17+ cells, CCL18+ cells and Foxp3+ regulatory T cells were prominent only in the lesional skin of BP. To further

investigate the function of M2 macrophages, we examined the mRNA expression and production of Th2-related chemokines from M2 macrophages in vitro, which showed a significant increase in the mRNA expression and production of CCL18 when stimulated by IL-4 or IL-13.[91]

RECURRENT APHTHOUS ULCERS

Regezi et al investigated the presence and distribution of macrophages (CD11c+ and CD68+) and macrophage-related dendritic cells (factor XIIIa+ and CD36+) in early and late aphthous ulcers associated with HIV infection. To substantiate a mechanism by which these cells may move from the vascular compartment to tissue spaces, we also investigated expression of ELAM (endothelial leukocyte adhesion molecule), ICAM-1 (intercellular adhesion molecule), and CD18 (leukocyte function antigen). Numerous CD11c+ and CD68+ macrophages were seen in early lesions, though larger numbers of CD68+ cells were present in older lesions. No significant increases in factor XIIIa+ dendrocytes were seen in either early or late lesions, though dendrocytes appeared enlarged. CD36+ cells and CD18+ leukocytes were more numerous in early than in late aphthous ulcers. ELAM and ICAM expression was most intense on endothelial cells in early aphthous ulcers, with staining intensity fading toward the lesion periphery. Control specimens showed weaker ELAM and ICAM staining than did the ulcer specimens. Keratinocytes did not express ICAM. By virtue of their numbers, macrophages and macrophage subtypes appear to have a significant role in both the early and late stages of this disease. Although factor XIIIa-expressing dendrocytes may not have been more numerous in the ulcers, they appeared to be "activated" because of their prominence in the lesions and their occasional co-expression of CD68 antigen (KP1+). They may have a minor role in antigen processing, phagocytosis, and fibroplasia. ELAM and ICAM expression by endothelial cells provides a mechanism by which macrophages and other leukocytes can be recruited to the site of the lesion.[92]

CONCLUSION

Apart from having physiologic roles in tissue homeostasis and normal development, they also take part in the progression of various chronic inflammatory conditions, like lichen planus, disease processes. Tumour associated macrophages are also hypothesized take part in tumour angiogenesis and metastasis. Hence, this gives a ray of light towards utilizing them as therapeutic targets in the treatment protocols of such lesions and conditions.

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