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The Role of Tumor Necrosis Factor-alpha (TNF-α) in the Pathogenesis of Oral Diseases

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Abstract

Tumor necrosis factor-alpha (TNF-α) is a proinflammatory cytokine produced by various types of cells in the body. These cells are essential for the normal function of the immune system and play a critical role during infection and inflammation. TNF-α plays a crucial role in regulating various physiological functions of cells. Also, this cytokine mediates immune and inflammatory responses. Many cytokines expressed due to inflammatory diseases impact bone loss by increasing osteoclast differentiation and activity. TNF-α can either have protective or destructive effects, depending on the tissue/cell types from where it is secreted and the downstream signaling mechanisms by its receptors. Elevated or dysregulated expression and secretion of TNF-α could also contribute to pathological conditions. Chronic inflammatory disorders caused due to increased local production of TNF- α, include periodontal disease, inflammatory arthritis, and aseptic periprosthetic osteolysis, which involve bone loss in joints and teeth. Some oral diseases such as recurrent aphthous stomatitis, Behcet's disease, chronic periodontitis, and Sjogren Syndrome are also related to TNF-α imbalance. FDA-approved TNF blockers in the United States include Remicade (infliximab), Enbrel (etanercept), Humira (adalimumab), Cimzia (certolizumab pegol), and Simponi (golimumab). These blockers suppress the immune system via blocking the activity of TNF-α. FDA-approved and licensed anti-TNF-α medications for treating systemic diseases in the United States include Infliximab, Adalimumab, and etanercept. Here, we reviewed our current understanding of TNF-α and its blockers on immune- and inflammatory-mediated effects.

Keywords: TNF-α; TNF-α Blockers; Oral Diseases; Periodontitis; Arthritis

Introduction

Cytokines are small proteins that almost every cell in the body produces. They are involved in the immune response. They also have a critical role in the inflammatory response. The proinflammatory cytokines activate the immune cells. They are also involved in the process of releasing other cytokines [1]. Estrogen suppresses TNF -α production [2], and several studies have shown the increased levels of inflammatory cytokines (TNF- α, Interleukin -1, -6, and Interferon-gamma) due to estrogen deficiency [3,4]. High levels of these inflammatory cytokines (e.g., TNF- α) contribute to bone loss by disrupting the balance between diminished osteoblastic bone formation and accelerated osteoclastic bone resorption activity in postmenopausal osteoporosis and other inflammatory diseases periodontitis, arthritis, etc. [5-7]. Carswell and his colleagues in 1975 introduced tumor necrosis factor-alpha (TNF-α). They named the tumor necrosis factor based on its necrosis effect on some tumors [8]. The first recognized TNF-α producing cells were macrophages [8], but later it was found that the secretion of this cytokine is not limited to macrophages. T-cells, B cells, neutrophils, and non-immune system cells such as fibroblast and endothelial cells can also be TNF-α producing cells [1,9]. Thus, TNF-α is a proven effective proinflammatory cytokine having diverse effects on various cell types.

TNF-α is also known in other names such as cachectin and endotoxin-induced factor [10]. It regulates infectious, inflammatory, and autoimmune events [11,12]. The significant part of TNF-α in several normal signaling pathways from proliferation to programmed cell death has been shown [13]. In the inflammation process, TNF-α induces the secretion of prostaglandin, which leads to vasodilation [14,15]. The role of TNF-α in the development of in vivo immune response was studied in TNF-α knockout mice. In the absence of TNF-α, mice demonstrated reduced contact hypersensitivity responses and a complete lack of B-cell follicles and humoral immune response [16]. We reviewed the following in this review: A) structure of TNF-α and its receptors, B and C) the potential association of TNF-α with bone loss, oral and other systemic diseases; D) Anti-TNF-α medications, E) Discussion, F) Conclusions

Structure of TNF-alpha and its Receptors

TNF-α belongs to the lymphotoxin (LT)/TNF family. Lymphotoxin (LT) is another superfamily member and has many similarities to TNF-α. Lymphotoxin (LT) was known as tumor necrosis factor-beta (TNFβ) for many years. After several changes between these two names, it changed to lymphotoxin alpha (LT-α) [17]. TNF-α exists in two bioactive forms: transmembrane TNF (tm- TNF-α ~26kDa) and the soluble TNF (s- TNF-α; ~17 kDa). The transmembrane TNF is also abbreviated as m-TNF-α [18-20]. The tm-TNF-α is a precursor of the s-TNF-α is expressed on the surface of several cell types, including activated macrophages and lymphocytes. The cleavage of tm-TNF-α produces the s- TNF-α form by a metalloprotease TNF-α converting enzyme (TACE). This proteolytic cleavage generates an N-terminal fragment of the TNF-α on the cell surface [21]. An increase in circulating s- TNF-α was related to the expression levels of TACE in atherosclerotic lesions of apolipoprotein E-deficient mice [22]. These fragments (s- and tm-TNF-α) initiate cellular signaling events via binding to type 1 or type 2 receptors on the cell surface; receptors are tumor necrosis factor receptor 1 (TNFR1; p55) and tumor necrosis factor receptor 2 (TNFR2; p75). Both tmTNF-α and s- TNF-α reacts with TNFR1 and TNFR2 (10), (Schematic diagram in Figure 1).

It was shown that s-TNF-α binds predominantly to TNFR1 and plays a vital role in the inflammatory immune response. In comparison, tm-TNF-α interacts primarily with TNFR2 and mediates cellular proliferation, survival, and other biological effects [23]. TNF-α has a role in the regulation of bone homeostasis and has been shown to have multiple effects on the differentiation of osteoblasts. It inhibits osteoblast differentiation via interfering bone morphogenic protein signaling [24,25]. It has also been shown that TNF-α induces Dickkopf-1 (DKK1) protein, affecting the differentiation of mesenchymal stem cells into osteoblasts and, hence, bone formation [24,25]. The pathogenesis of inflammatory bone diseases (e.g., periodontitis and rheumatoid arthritis) is associated with TNF-α levels and osteoclast bone resorption. Also, repression of osteoblast differentiation and bone formation is likely an additional mechanism when excess TNF-α is produced under inflammatory conditions [26,27].

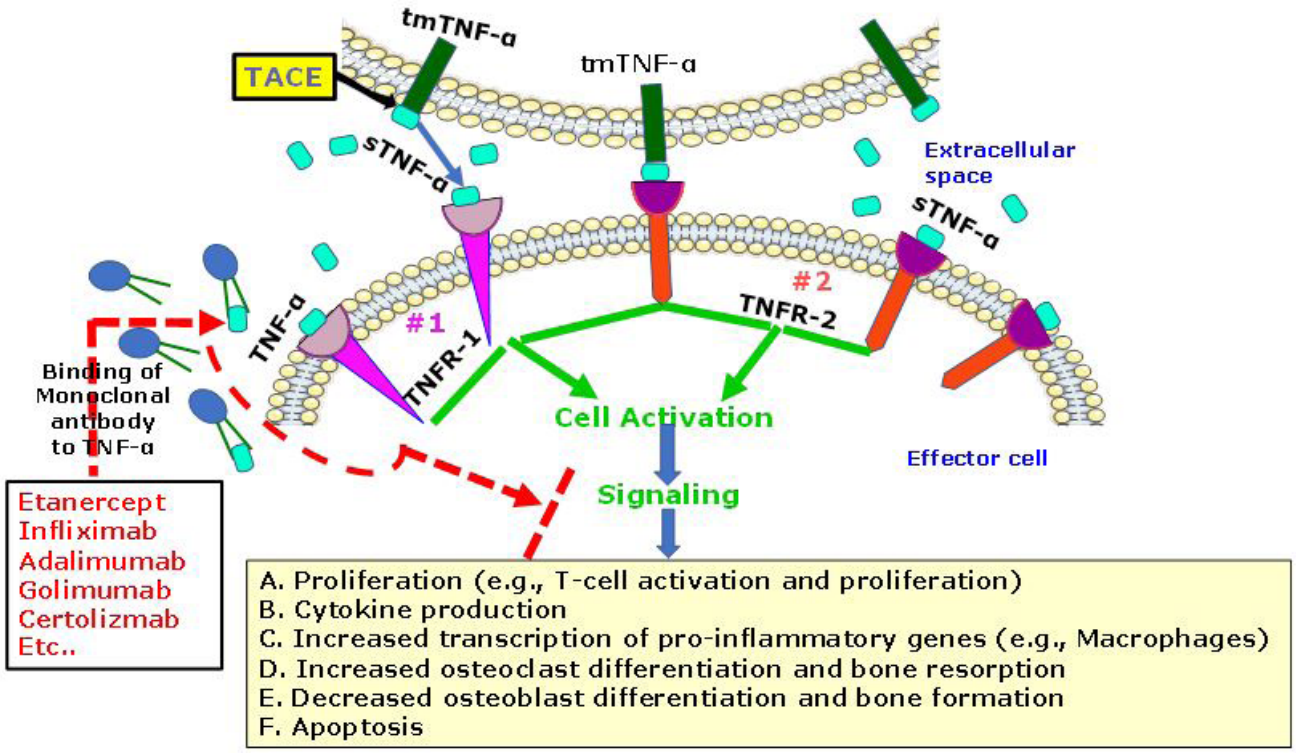

Figure 1: Possible Biological effects of TNF-α mediated signaling pathways

Transmembrane TNF-α (tm-TNF-α) is a polypeptide with 233 amino acids (~26kDa) is cleaved between alanine and valine amino acid residues by an enzyme called TNF-α-converting enzyme (TACE). The resulting soluble sTNF-α with 157 amino acids (~17kDa) is released from the membrane. tm-TNF-α or sTNF-α are biologically active forms and mediate signaling via binding to TNFR1 (#1) or TNFR2 (#2).

Both TNFR1 and -2 mediate various physiological and pathological responses required for healthy and diseased conditions. The scheme shows the cellular signaling pathways play a vital role in proliferation, cytokine production, immunity, osteoblast differentiation, osteoclast resorption, and apoptosis via the activation of specific downstream signaling processes. The downstream signaling mechanism for a given activity is dependent on the cell type.

TNF-α therapy is provided dependent on the clinical situation. Five anti-TNF-α agents are indicated in the scheme (red). Among these five, infliximab, etanercept, and adalimumab have been clinically widely used. These agents bind to either s- or tm-TNF-α and block the effector cell signaling processes and the resultant effect of TNF-α (broken red arrow).

TmTNF-α can act as a bipolar molecule that conducts signals both as a ligand and a receptor in a cell-to-cell contact-dependent manner, i.e., tm-TNF-α can mediate the forward signaling cells via cell-to-cell communication (Scheme in Figure 1; TNFR-2 binding to tm-TNF-α of a neighboring cell). Tm-TNF-α can also transmit the reverse (outside-to-inside) signals back into the cells bearing tm-TNF-α, subsequently binding to its native receptor [28]. Reverse signaling triggered by tm-TNF-α and TNFR2 interaction played a significant role in maintaining tumor cell survival and metastasis [28]. s-TNF-α has been implicated in the steps of tumor development such as immune responses, tumorigenesis, proliferation, angiogenesis, and metastasis. BRAF is a human gene that encodes a protein called B-Raf. Besides its role in tumor development, s-TNF-α also induces drug resistance to BRAF inhibitors [29,30]. Studies by Zhang et al. demonstrated that the expression of tm-TNF-α was correlated positively with the chemoresistance to anthracycline chemotherapy in breast cancer patients. Suppression of the reverse signaling by using a mutant form of tm-TNF-α with intact intracellular domain in a xenograft mouse model significantly enhanced the efficacy of doxorubicin [31]. Although s-TNF-α and tm-TNF-α are bioactive molecules, a detailed, comprehensive analysis is required to determine their bioactivities in terms of their binding specificity to TNFR1 and TNFR2 and signaling capacity. Identifying pathways will provide a novel therapeutic target for anti-TNF therapy related to s- or tm-TNF-α bioactivity.

The potential association of TNF-α with diseases associated with bone loss

Bacterial infection and its interaction with the host immune system led to periodontal diseases, including gingivitis and periodontitis. Consequently, the gingival epithelium also releases the proinflammatory cytokines besides the inflammatory mediators produced by the immune cells. Studies have linked periodontal diseases to cardiovascular diseases [32-34], rheumatoid arthritis [35,36], and cancers, including digestive, breast, prostate, and bladder cancers [36-40].

Periodontal disease: Periodontal disease is an inflammatory disease in acute or chronic form. Gingivitis is an inflammatory situation limited to gingivae. When the inflammation goes to the other supporting periodontal tissues, it is called periodontitis [41]. The prevalence of gingivitis is more than 80% of the population (children and adults). For periodontitis, the majority is related to age. It can be as low as 9% (for 18-24 years old) to more than 60% (for 65 years old) [42]. In chronic periodontitis, destruction of supporting tissues occur. It can be soft tissue like connective tissue or hard tissue like alveolar bone.

The initiation of this disease is related to specific anaerobic bacteria. But the host response to the bacteria is critical in the bone destruction of chronic periodontitis. The body's reaction to lipopolysaccharide (LPS), which is an endotoxin present in bacteria's outer membrane, causes the immune cells (T cells and macrophages) to be recruited to the area [43-45]. LPS/TLR pathways are activated either by mono- or polymicrobial infections, increasing the expression of proinflammatory molecules such as IL-6, IL-8, IL-1β, and TNF-α by the immune cells. Elevating cytokine levels are one reason for periodontal tissue destruction in chronic periodontitis [42]. IL-1 and IL-6, and TNF-α have been implicated in osteoclastogenesis, osteoclast activity, alveolar bone loss. Progression of bone resorption can eventually lead to tooth loss [46]. TNF-α induces osteoclast formation and activity and reduces osteoblast differentiation and bone formation, shifting the balance towards more bone resorption without replacing the new bone formation [47]. LPS induced TNF-α production involves the ERK signaling pathway, and IL-10 synthesis requires JNK and/or p38 [48]. Periodontitis is not caused only by pathogens; the consequence of uncontrolled immune response and oxidative stress also impacts periodontal tissue damage. In vitro, in vivo, and human studies showed host modulation therapy seems a definite therapeutic approach to reach the clinical benefit level [49].

Most of the current treatment plans focus on treating bacterial infection, which is not practical for all patients. However, the host modulating treatment like anti-TNF-α can be a future direction for patients who poorly respond to the conventional treatment [50]. The only FDA-approved host modulating treatment for periodontitis is the sub-antimicrobial doxycycline. Reducing the inflammatory biomarkers and collagenase activity has been seen with sub-antimicrobial doxycycline treatment [51]. In different studies, the efficacy of the anti-TNF-α medications in decreasing periodontal tissue destruction has been shown. However, more clinical trials are essential to establish [50,52].

Chronic inflammation is also associated with carcinogenesis via the inflammatory mediators produced during periodontitis. The species of highly invasive anaerobic bacteria can transform the cells directly. Bacteria found in the sulcus or periodontal pocket could induce NF-kB mediated actions, facilitate cell survival, initiate oncogenic pathways, reduce the expression of proapoptotic proteins, increase cell migration and invasion. An increase in the levels of EMT-related proteins could enhance the metastatic processes [53-55]. The actual mechanisms by which the bacteria-mediated carcinogenesis occurs and their tumorigenic effects need further elucidation.

Rheumatoid Arthritis (RA) and Ankylosing spondylitis (AS): RA is a systemic inflammatory disease that affects the joints, though the extra-articular involvements are common [56]. RA got more attention because of periodontal disease. Periodontal diseases and RA have several similar characteristics [36]. Periodontal diseases are more prevalent in RA patients. In patients with RA, oral health issues should be more thoroughly scrutinized [57]. Patients with advanced RA have a higher score for tooth loss [58]. In addition, they develop more significant temporomandibular joint (TMJ) and periodontal problems than patients who have periodontal disease and no RA [59]. TNF- α causes bone destruction, and the inhibition of TNF- α lags the bone loss processes in RA patients [60, 61]. Also, bone formation is substantially diminished at the erosion site of RA [62]. In a mouse model, *P. gingivalis* has been demonstrated to trigger arthritis and aggravated. *P. gingivalis* demonstrated a detrimental effect in inducing citrullination, systemic inflammation, and osteoclastogenesis, leading to bone damage [63,64].

The other chronic inflammatory is ankylosing spondylitis (AS), typified by sacroiliitis, spondylitis, and peripheral arthritis of large joints. TNF-α expression was found at the sac-

roiliitis site, and this cytokine's crucial role in AS pathology was identified via inhibition of TNF-α in AS patients. This inhibition reduced signs and symptoms of AS with a better physical function and quality of life in these AS patients [65,66]. Studies with c-fos –/– heterozygous Tg197 TNF transgenic mice (c-fos–/–hTNFtg) demonstrated that arthritic erosions could not develop in the absence of osteoclasts. Inhibition of osteoclast differentiation and activity changes damaging arthritis to a non-damaging one [67]. The association between AS and oral diseases like periodontitis has been shown in several studies [68-70]. The higher level of TNF-α is considered one of the reasons for arising AS and periodontitis [70,71]. The other oral disease related to AS is an oral ulcer that is significantly higher than the control group [70].

The potential association of TNF-α with other Oral and other systemic diseases

Recurrent aphthous stomatitis: Recurrent aphthous stomatitis (RAS) is defined as recurring ulcers in the oral cavity (several times during the year). RAS prevalence is high in developed countries, and most people experience RAS before 30 years [72]. Aphthous ulcers can be seen as a solitary disease or combined with other conditions like Behcet's disease, Crohn's disease, or aphthous related to HIV disease [73]. There is no specific laboratory test for diagnosis. So, other conditions should be ruled out before diagnosing RAS. The clinical and history evaluations can be helpful in the diagnosis process [74]. The peak for RAS onset is during adolescence (10-19 years old) [75]. The etiology of this disease is unknown. Several factors are related to RAS-like trauma, genetic predisposition, nutritional deficiencies, and stress. The process of RAS led to ulcer formation, and the aim of the treatment is to reepithelization and inflammation [76]. The imbalance of the immune system is also responsible for arising this disease. The cell-mediated immunity, e.g., T cells (TNF-α producers), is elevated in this disease [77]. TNF-α is also related to new lesions occurring [72]. Moreover, the salivary TNF-α level in RAS patients is higher (serum and saliva) in the active phase of the disease [77,78]. Controlling the TNF-α production is an effective treatment in RAS [78]. Balancing TNF-α decreases inflammation, and it can change the whole process from arising RAS [76]. At this time, there is no standard protocol for the duration of therapy with anti-TNF-α medications [72].

Behcet's disease: Behcet's disease (BD) is a chronic vasculitis involving multiple organs with unclear causing factors [79]. The monocytes of BD have shown higher secretion of some cytokines like TNF-α [80]. There is a significant clinical difference between the involvement of males and females. However, women showed less mortality in comparison to men. Furthermore, females show fewer symptoms in organ involvement [79]. Oral manifestation of BD is usually the first symptom of this disease. They arise as recurrent aphthous ulcers with a recurrence of three times a year or more. The ulcers can be multiple or single. The lesions can be so painful that they prevent the patients from eating. Like RAS, based on the type of lesion (minor, major, herpetiform), they can be healed with or without a scar. These lesions can be seen on different oral cavity parts like gingival tissues, palate, and tongue [81]. High dosage immunosuppressive medications are administered in patients with vital organ injuries. It was adequate for the severe and refractory BD [82, 83]. The effects of the anti-TNF drug on BD have been evaluated. Although, the main administration for anti-TNF medications is recommended for patients with eye involvement [84]. The limitation of the studies for oral lesions is related to the low number of patients and limited time for the follow-up. [80,82]. The anti-TNF-α drugs for mucocutaneous ulcers in BD are effective when the other treatments fail [85].

Sjogren Syndrome: Sjogren syndrome (SS) is an autoimmune disease with lymphocytic infiltration to the exocrine glands [86]. The lymphocytic infiltration includes T-cells and B-cells. Overexpression of TNF-α in saliva and serum has been seen in SS [87]. Also, the intraglandular TNF-α is associated with acini destruction [88]. Lacrimal glands (eyes) and salivary glands (mouth) are the two main affected glands. So, dry eyes and dry mouth are common symptoms of this syndrome. This disease is more common in females and the middle ages [89]. In the absence and presence of other systemic diseases, it is called primary and secondary SS.

The systemic diseases accompanying SS are lupus erythematosus and rheumatoid arthritis [86]. Xerostomia (dry mouth) causes difficulty in eating and talking in SS patients. Another complication in the oral cavity is the higher prevalence of dental decay due to decreased saliva [90]. Initiating early treatment is essential to prevent the complication of SS. Treatment is mainly based on reducing the symptoms and decreasing the complications. The therapy focuses on increasing salivary secretion, preventing dental decay, periodontal disease, and oral infection [89]. Several anti-TNF medications like infliximab and etanercept are on the clinical trial for SS [91]. Based on the pathogenicity of SS, anti-TNF-α medications are a promising treatment for the future.

Anti-TNF-α medications

Currently available, the five TNF-α antagonists include etanercept, infliximab, adalimumab, golimumab, and certolizumab pegol. Table 1 provides the list of inhibitors, their binding specificity to TNF-α and/or LT-α, and possible therapy for different inflammatory diseases

1) Etanercept (Enbrel) is a soluble TNFR2 that can bind to TNF-α. Etanercept was the first approved medication for rheumatoid arthritis patients [92]. This antibody combines two extracellular parts of TNF receptor 2 (TNFR2) and Fc from human IgG1 [93]. Thus, etanercept can bind to both TNF-α and LT-α. But its binding to TNF-α is limited to the active form of TNF-α (trimer) [94].

2) Infliximab (Remicade), a chimeric monoclonal antibody, was first approved for human usage in Crohn's disease. Infliximab is a combined antibody from mice and humans. The medication constitutes about 75% of the human (constant region) and 25% of murine (variable region) [11]. It is also used to treat Ulcerative colitis, rheumatoid arthritis, ankylosing spondylitis, psoriasis, psoriatic arthritis, and Behçet's disease [95,96]. Infliximab affects active (trimer) and inactive (monomer) forms of soluble TNF-α. It also can lyse the TNF-α expressing cells [94]. In BD, infliximab was used for controlling eye involvement. Administration of infliximab showed significant and rapid remission in BD patients with ocular inflammation who experienced other treatments' relapse [97]. However, infliximab usage is a fast and efficient treatment for acute ocular inflammation; this medication cannot treat irreversible retinal damage [98]. There are other considerations in BD patients who have mucocutaneous ulcers. These patients are more predisposed to infection and especially tuberculosis. Therefore, if anti-TNF-α medication is used, the patient should follow up to prevent other conditions [82]. There are limited studies in the usage of infliximab and etanercept for SS patients. Also, there are no studies related to the usage of adalimumab in SS patients. Therefore, more studies are needed to elucidate the effects of anti-TNF-α drugs in SS patients [88].

Table 1: List of TNF-α inhibitors and their characteristics

TNF-α inhibitors (Brand Name)	Etanercept (Enbrel)	Infliximab (Remicade)	Adalimumab (Humira)	Golimumab (Simponi)	Certolizumab pegol (Cimzia)
Structure	Humanized structure	Combined mice and human structure	Humanized structure	Humanized structure	Humanized structure
Binding Specificity	TNF-α and LT-α	TNF-α	TNF-α	TNF-α	TNF-α
Effect on TNF-α expressing cells	No lysis	Lysis	Lysis	No lysis	No lysis
Used to Treat diseases	Rheumatoid, Juvenile Idiopathic, and Psoriatic Arthritis	Crohn's Disease, Ulcerative colitis, Rheumatoid and Psoriatic Arthritis, Ankylosing Spondylitis, Moderate to Severe plaque Psoriasis, and Behçet's Disease	Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic arthritis	Rheumatoid and Psoriatic Arthritis, Ankylosing Spondylitis, Ulcerative Colitis	Crohn's disease, Rheumatoid arthritis, Ankylosing Spondylitis, Moderate to Severe plaque Psoriasis

3 and 4) adalimumab (Humira) and golimumab (Simponi) are fully human antibodies used as immunosuppressive medications [99, 100] for rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis [101]. Adalimumab is an IgG1 monoclonal antibody with humanized structure. Adalimumab binds to TNF-α and prevents the interaction between TNF-α and its receptors. One of the advantages of adalimumab is subcutaneous administration [102]. Adalimumab has a higher affinity to TNF-α in comparison with infliximab and etanercept [72]. Body reaction against adalimumab is less because of this antibody's fully human and monoclonal structure [102]. However, adalimumab has a lysis effect on the cells with surface expression of TNF-α like infliximab [94]. Although the adverse effect profile of golimumab appears similar to other agents in the treatment of psoriatic arthritis, the longer-term safety profile of golimumab needs further elucidation [103].

5) Certolizumab pegol (aka Cimzia) is a Fab' fragment of a humanized anti-TNF-α antibody to treat inflammation and symptoms of Crohn's disease, rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Adalimumab, Golimumab, and Certolizumab pegol are used in adult patients who have obtained other medications that didn't work. Each compound can neutralize TNF-α; evidence shows different efficacy in treating these diseases.

Although Food and drug administration (FDA) have approved several anti-TNF-α medications for human usage, the most commonly used TNF inhibitors are infliximab, adalimumab, and etanercept [104]. All these anti-TNF-α medications work through attachment to TNF-α (s- and tm-TNF-α) and prevent the activation of TNFRs [9]. Infliximab, adalimumab, and etanercept bind to and neutralize s-TNF-alpha but exert different effects on tm-TNF-alpha-expressing cells [105].

Discussion

TNF-α is a proinflammatory cytokine that exerts various effects (physiological and pathological) on different cell types. An increase in the production of TNF-α results in bone loss by osteoclast activation, which contributes to several common diseases, including osteoporosis, periodontitis, and rheumatoid arthritis; osteoclast activation by excess TNF-α affect bone structure under these conditions. Bisphosphonates are often used to treat osteoporosis. Bisphosphonates (BPs) inhibit osteoclast activity and hence bone resorption. Therefore, these drugs are widely used for osteoporosis treatment. However, uncommon side effects including, atypical stress fractures and inflammatory eye disease, have been noticed. In addition, periodontitis is associated with BP-related osteonecrosis of the jaw [106]. The novel compound [4-(methylthio) phenylthio] methane bisphosphonate (MPMBP) was shown to have a therapeutic effect on inflammation-related bone loss in animal models [107-110]. However, the clinical impact of MPMBP needs further elucidation and more reports. We have previously demonstrated that anti- TNF-α and anti-TNFR1 blocks TNF-α mediated signaling involved in sealing ring formation and bone resorption by osteoclasts isolated from the bone marrow of long bones of mice [111,112]. However, our recent studies indeed have shown that TNF-α has the potential to reduce osteoblast differentiation and bone formation. TNF-α mediated effects on osteoblasts are inhibited by anti- TNF-α drugs, including etanercept and infliximab (unpublished observations). TNF-α gene silencing with topically applied siRNA nanoparticles has been developed as a calcium phosphate paste. The effect of this paste has been investigated in a rat periodontitis model in vivo [113]. Based on the available data, anti-TNF-α drugs have emerged as valuable therapeutic agents in treating many chronic inflammatory diseases. Therefore, the usage of anti- TNF-α drugs as a topical medication in the form of paste seems a promising approach in circumstances where excess TNF-α is produced (e.g., chronic periodontitis).

Conclusions

TNF-α elevation in the body is one of the underlying molecular mechanisms of several diseases. Host modulating treatments (like anti-TNF-α medications) are used for immune-mediated conditions. Several studies have shown that TNF-α therapy reduces osteoclast bone resorption. It has also been found to stimulate bone formation by osteoblasts in mice with rheumatoid arthritis via increasing Insulin-like 6 Peptide by polarized macrophages [114]. TNF-α inhibitors have been used for some conditions like rheumatoid arthritis for an extended period with successful results. The TNF-α imbalance was detected (systemically or locally) in some oral diseases, but there is limited information about anti-TNF-α medication and oral diseases. Using TNF-α inhibitors as a secondary line of treatment in severe oral conditions upon failure of other primary therapies can be life-changing. More clinical studies on the applicability of anti-TNF-α medications are needed for developing new treatment plans for oral diseases.

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