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REVIEW ARTICLE

The Role of TNF- α as a Proinflammatory Cytokine in Pathological Processes

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Abstract: TNF- α is a member of the vast cytokine family being considered a proinflammatory substance produced many by macrophages and other cells belonging to the innate immunity, many of them classified as indeed Antigen Presenting Cells (APCs) involved in the complex chemotactic process of activation of the adaptive immunity. The aim of this work was to accomplish a literature review concerning the main pathologies that have TNF- α as a modulating agent in other to bring light to the main interactions present in the inflammation installed.

Keywords: Tumor necrosis factor, Inflammation, Cytokine(s), Leucocytes, Antigen Presenting Cells (APCs), Interferon (IFN).

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1. INTRODUCTION

Cytokines are classified as a category of small proteins (~5–20 kDa) essential for cell signaling; modulating the complex functions of the immunologic system by either enhancing or inhibiting the behavior of other nearby or distant cells, Cytokine gene expression: part of host defence in pulpitis [1]. This family of substances is vast, and the way they act *in vivo* still challenge scientists. Their most studied members are the Interleukins (IL), Interferon (IFN), Growth Factor (GF), Colony-stimulating Factor (CSF), Chemokines (CKs), and Tumor Necrosis Factor (TNF) [2]. Tumor Necrosis Factor alpha (TNF- α) has been studied for years and exhaustively described in the scientific literature [3]. It is regarded as a proinflammatory substance produced mainly by macrophages and other cells belonging to the innate immunity, many of them classified as Antigen Presenting Cells (APCs) involved in the chemotactic process of activation of the adaptive immunity in association with interleukins, especially IL-1 α , IL-1 β , IL-6 and IL-8 (1), integrating the innate and adaptive immunities [4].

Many studies have described the role of TNF- α in infectious diseases, as well as in chronic and acute inflammations [5]. It was firstly identified in the serum from mice following administration of bacterial endotoxins, which resulted in cyto-

toxic or cytostatic effects to human cells, leading to hemorrhagic necrosis, and performing, in experiments with mice, carcinogenic cell regression [6].

The excessive production of pro-inflammatory cytokines, which is observed in inflammatory conditions, not only increases the immune response of the host organism, but also causes deleterious effects that are able to modulate hemodynamic regulation and metabolic control [7]. Therefore, it is only expectable that different pathologies have, in common, the influence of TNF- α in the course of their establishment and development. Therefore, the aim of this work was to accomplish a literature review concerning the main pathologies that have been described in the literature concerning TNF- α as a modulating agent.

2. LITERATURE REVIEW

Tissues of the immune system are formed by the lymphoid organs, also called primary or central tissues, within which T and B lymphocytes mature, becoming competent cells to respond to the antigens; and peripheral (or secondary) lymphoid organs, where secondary immunological responses to the aggressor agents get started [8].

The appropriate immune response depends on the balanced cell-to-cell communication, and also on the overall conditions of the host organisms, including nutrition, environmental matters, as well as genetic programming. Cell recruitment and arrival on the inflamed sites is partially obtained by the

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synchronized synthesis and function of cytokines and their action on their counterparts: The receptors located mainly on the cell membrane; without which they would never respond. In fact, cytokines define the subpopulation that will be recruited in each step of the immune response, stimulating recruitment or inhibiting production and release [9].

2.1. Tumor Necrosis Factor Alpha Receptors

TNF- α is produced as a pro-hormone substance constituting 233 amino acids. It is closely linked in the cell membrane of many cell types, and then processed to a 157 residue mature protein by cleavage of a 76 residue signal peptide. Not until 1975 was TNF- α identified as a soluble factor that caused necrosis of tumors, and thereafter came its designation [10]. It had initially been referred to as Cachectin or Differentiation Inducing Factor (DIF), with two bioactive forms: transmembrane TNF- α (tmTNF- α) and soluble TNF- α (sTNF- α) [11 - 14]. The latter seem to be able to bind the ligand and inhibit the cytotoxic activities of TNF- α [15].

Both receptors are in fact proteins. Their extracellular portions link to TNF- α , constituting a receptor family with four characteristic domains with cystine residues regularly spaced [16]. Their proteins seem to be residual fragments of the extracellular regions of the type 1 and type 2 membrane-bound receptors for TNF alpha [17].

Later on, the encoding genes of cachectin and TNF- α were confirmed as identical molecules with no need for different meanings (4- Caput, 1986). Once produced and released into the blood stream, TNF- α bind to its two main receptors namely: TNF receptor 1 (TNF-R1), (55-kDa) and receptor 2 (TNF-R2), (75-kDa) [18], distinct from each other, but expressed in many different cell lineage surfaces. R1, corresponds to the majority of the TNF- α activities, being a ubiquitous membrane receptor found in most cell types which rapidly attaches to TNF- α . Receptor 2, on the other hand, is initially expressed intensively by T cells and endothelial cells, for rapid and efficient response by recruiting or inhibiting specific cell types when necessary, such as lymphocytes and clastic lineages [19 - 21]. The former is activated by either sTNF- α or tmTNF- α ; while the latter is preferentially activated by tmTNF- α [22, 23]. Sometimes, however, a small degree of overlap and cross talk between both receptors may occur, despite being structurally different. The stimulation, however, does not seem to be altered. Anyway, the binding of TNF- α to receptor 1 may activate the transcription factor NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells, regulating cytokine production, and modulating inflammation and apoptosis, depending on the immunological need [24].

Protein Kinases (PTKs) are enzymes that regulate the biological activity of proteins by phosphorylation of specific amino acids with ATP as the source of phosphate, thereby inducing a conformational change from an inactive to an active protein. Although TNF- α receptors do not have activity of intrinsic protein kinase, they respond very quickly to TNF- α stimulation, causing phosphorylation of several distinct proteins [25].

2.2. Tumor Necrosis Factor Alpha Association with Interleukins

The interaction between the cytokine family members are necessary steps for the establishment and development of inflammation, simply because of the amplification of the responses produced by each of their kinds. In this context, TNF- α is usually produced simultaneously with interleukins potentializing pro-inflammatory vascular and cellular alterations [26]. Therefore, TNF- α and IL-1 are usually produced together as a prompt response to bacterial infections. Together they both modulate pro-inflammatory signals by coordinating vascular and cellular changes in the immune system, activating many of the components present in the innate immunity, increasing the expression of chemokines and adhesion molecules, critical for the recruitment of neutrophils from the blood, initiating the immune first lineage prompt response in the host [27 - 29].

TNF- α biological main effect tends to integrate both innate and adaptive immunities, although this designation is merely didactical, due to the reciprocal bioactivation of both sort of immunities, which clinically means that they are so interacted that could not be studied as separate matters [30]. Initially, TNF- α potentializes T and B leukocytes activation, which also affects *via* feedback chemotaxis, macrophages and Natural Killer (NK) cells, both Antigen Presenting Cells (APC) belonging to the innate immunity. Such cell-to-cell interaction leads to a cascade of events, also stimulating the adaptive immunity to interact, which is represented mainly by T and B lymphocytes, responsible for antibody production [31]. TNF- α also triggers Prostaglandins (PG) production, increasing fever induction, and the release of the acute inflammation phase proteins, such as C-Reactive Protein (CRP), gene expression of cytokines and chemokines, and endothelial cell activation [8], contributing significantly to vascular changes for increased blood flow in the site of the injury. Some studies have similarly reassured that TNF- α , in association with other interleukins, potentiate bone resorption capacity [32, 33].

2.3. Tumor Necrosis Factor Alpha and Genetic Polymorphisms

The gene that encodes TNF- α is located in the short arm of chromosome 6, in the 6p21.3 region. Single Nucleotide Polymorphisms (SNPs) are the most common variation in the human genome that differentiate from the rare mutations because they present frequency of at least 1% of the less common allele in the population. One SNP takes place in virtually 1 out of a thousand base pairs and their most common replacement (2/3 of the overall) is of one cytosine by a thymine (C/T) [34, 35]. One SNP may influence the genic product by different manners: (i) variations in un-translated region 5' (5'UTR - 5' Un-translated Region) may modify the mRNA translation; (ii) variation in un-translated region 3' (3'UTR - 3') may affect the cleavage, stability and the transport of mRNA, thus altering protein productions which clinically may imply in differentiated cell functions, for better or for worse.

SNPs may occur in the coding region, or in the regulatory region of the gene, leading to changes in the amino acid sequence of the encoded protein, or its production rate. For

being bi-allelic, SNPs can be detected by using techniques that discriminate any different combinations in the nucleotides Adenine (A), Thymine (T), Cytosine (C) and Guanine (G). Among the SNPs, the -308 G/A (rs1800629) in the promoter region is described as being able to increase the gene expression and therefore the level of TNF- α production due to the transition from wild-type G allele to the variant A allele [36].

TNF- α is encoded in the promoter region -308 G/A (rs1800629) and admits three different kinds of genetic profiles: The homozygous form G/G, and the mutant variant forms G/A and A/A. The wild type genetic profile G/G is most commonly found in a specific population studied, usually associated with low level TNF- α -producing individuals. The mutant form, G/A, on the other hand, is related to intermediate production, while the rarer form, A/A, is associated with high level TNF- α - producing individuals. Expectable as it seems, it is possible to speculate that the presence of such genetic polymorphisms could exacerbate the inflammatory responses depending of the genetic individual profile, modulating the course of the disease, and therefore the immune response of the organism [37]. Pathologies such as pulpitis and periodontitis have recently been investigated as for the changes in inflammatory intensity due to the genetic profile. Table 1 exemplifies the effects of the genotypes in the inflammatory response.

Table 1. Effects of the genetic profile on the inflammatory response.

G/G	G/A	A/A
Low producing profile	intermediate producing profile	High producing profile
Low inflammatory response	Moderate inflammatory response	Severe inflammatory response

2.4. Tumor Necrosis Factor Alpha and Periapical Lesions

The two most common lesion types in the periapical area are granulomas and periapical cysts [38 - 40]. Both lesions are usually expansible, and their establishment costs to the organism more than just bone resorption, but also the differentiation, recruitment and arrival of different cell types on the injury site, depending on the inflammatory phase inflicted by them.

The origin of the periapical lesions is associated with bacterial contamination and posterior necrosis of the dental pulp. The progress of this process usually goes through four well determined stages: **a)** exposure of the dental pulp to the oral cavity; **b)** subsequent penetration and bacterial colonization; **c)** pulp inflammation and finally; **d)** necrosis. The inflammatory response involves leukocyte-activation, initially neutrophils from innate immunity, which will chemotactically recruit and signalize more sophisticated leukocytes from the adaptive immunities [41 - 43], resulting in osteoclastogenesis and the formation of osteolytic lesion around the dental apex, easily observed in routine periapical radiographs, especially in long term chronic lesions [44, 45], leading to bone resorption, for which there is no expectation of neoformation or cure without endodontic therapy [46].

The very nature of the periapical lesions results, most of the times, in bone resorption, observed by the local production of PGE₂, IL-1 β , and TNF- α [47]. The interaction of prostaglandins, interleukins and TNF- α seems to be potent enough to cause fast bone destruction in the periapex, as well as granulomatous tissue formation, which are typical features of the periapical lesions [48].

3. TUMOR NECROSIS FACTOR ALPHA AND CARDIAC INJURIES

Not until 1990 was TNF- α recognized as a participant in congestive heart failure (CHF), when it was demonstrated that its high circulating seric levels were linked with the final stage of heart failure [49].

Heart failure is in general related to myocyte damage with prior injury history. The main responsible are habits such as Alcohol, smoking and sedentarism, factors that increase cardiac failure risk. Hearts in normal conditions do not express the TNF- α protein or its transcripts. On the other hand, failing hearts do express TNF- α not only because of chemical mediators unleashed by blocked vessels, but also because of reduced contractibility of the myocytes in its presence. The elevation of plasmatic seric levels of cytokines acting as pro-inflammatory mediators during and after myocarditis and infarction corroborates in this sense [50].

A series of seminal studies demonstrated that normal human hearts did not express TNF- α protein or transcripts, whereas end-stage failing hearts expressed TNF- α as assessed by Enzyme-Linked Immunosorbent Assay (ELISA), Northern blot, and immunohistochemistry [51]. The process is complex and involves interactions of interleukins and chemokines, and in many situations, the real cause remains unclear, which made researchers investigate the role of cytokines in the process. It is clinically known that failing hearts do have some degree of inflammatory cell infiltrates, a fact that can be expected as a source of TNF- α , in cardiac myocytes and nonmyocytes [52, 53]. The three most commonly involved cytokines concerning heart failures are TNF- α , IL-1, and IL-6. With synergic interactions, they are all capable of amplifying the inflammatory response of preexistent cardiac alterations, especially those that obliterate blood vessels. Bacterial endotoxin Lipopolysaccharide (LPS) has been related as one of the most powerful TNF- α inducers, even with very small circulating amounts.

In a study conducted with hamsters, TNF- α inhibited the contractility of isolated papillary muscles, in a concentration-dependent and reversible manner [54]. Later on it was suggested that the individual susceptibility of myocardium infarction could be related to genetic factors. From that point on, researchers began studying the influence of individual genetic profiles in the development of cardiac failures.

There have been growing evidence that the G/A polymorphism in the -308 promoter region of the TNF- α gene may affect the transcription, expression, and the consequent biological activity of TNF- α , indicating that the individual genetic profile may play a determinant role in its clinical behavior [55]. A study [56] concluded that Italians with the mutant gene (A) polymorphism, high producing (A/A) and

intermediate producing genotype (G/A), had a higher risk of ST-segment elevation myocardial infarction than others who did not express polymorphisms. It was also observed that the reperfusion therapy after myocardium infarction has been associated with episodes of ischemia/reperfusion injury or no-reflow, which is related to TNF- α , as well as myocardium stunning and left ventricular systolic dysfunction [57, 58].

TNF- α does not encounter barriers once it is produced and released; reaching cell receptors wherever blood irrigates. It seems to play a determinant role in cardiac injuries, although its action in most cardiac cell type is still unclear. Anyhow, TNF- α -activated signal transduction pathways have been postulated to act on adverse ventricular remodeling after myocardial infarction, as well as being a major contributor during the development and progression of heart failure [59].

4. TUMOR NECROSIS FACTOR ALPHA AND ARBOVIRUSES

Arboviruses have also been researched in relation with TNF- α alterations. Increased levels of TNF- α have been associated with Dengue virus (DENV) infection. The main symptoms of DENV infection is dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) [60]. It is known that TNF- α affects the vascular Endothelial Cells (EC), as well as endothelial leukocyte interactions, promoting disruption of cell-cell junctions, disassembly of focal adhesion complexes, and morphological changes leading to increased vascular permeability [61]. With all of such alterations, this potent cytokine is able to stimulate bleeding, one of the main problems concerning this disease. Seemingly, altered serum levels have also been found in patients bearers of Zika virus [62].

5. TUMOR NECROSIS FACTOR ALPHA AND ALZHEIMER'S DISEASE

Alzheimer's Disease (AD) is the main cause of dementia worldwide. It represents one of the most serious and severe health problems for the elderly. There are a number of cytokines involved in the modulation of neuroinflammation, but TNF- α seems to play a pertinent role, particularly in the peripheral and central nervous system of adults, despite the fact that healthy adults do have low levels of it. Serum levels of this cytokine is significantly higher in blood¹⁴ and central nervous system [63] of patients with Alzheimer diseases, and clinical and animal studies have shown that there seems to be a link between high TNF- α serum levels in the brain and AD [64].

6. TUMOR NECROSIS FACTOR ALPHA AND CANCER

TNF- α is highly involved in patients with cancer, and clinically it can be easily noticed by abnormal amounts of it in the seric levels. Its effect on the tumorous cells seems to be the formation of oxygen radicals inside the cells exposed to it [65]. It is only natural and expectable that the inflammation caused by the growing tumor, and the chemotactic effects and defects due to it, implicates in cytokine production. Since TNF- α has

shown abilities to inhibit tumor growth, its anti-tumour effect *in vivo* has been hypothesized to be mediated by selective damage to tumour-associated vasculature, by decreasing blood flow [66], and therefore, the systemic administration of TNF- α began to be applied. However, severe toxicity was reported. It seems that humans tolerate a maximum of 8-10 μ g kg⁻¹ body weight of systemically administered TNF- α before life-threatening toxicities set in. Tumor regression on the other hand, demands doses of nearly 400 μ g kg⁻¹, making it impossible for clinical use [67 - 69].

Still concerning cancer, some studies do reveal that the ectopic expression of TNF- α at the site of malignancy induces strong and long-term tumor regression [70, 71]. On the other hand, a "dark side" of this cytokine has raised in apparent contradiction to its name. There has been increasing evidence that, especially in middle and old age, TNF- α functions are concerned with the promotion and progression of tumors, rather than with protection and worse still; the evidence includes that TNF- α is involved with proliferation, transformation, angiogenesis, invasion, and metastasis in many types of cancers [72].

7. TUMOR NECROSIS FACTOR ALPHA AND RHEUMATOID ARTHRITIS

Rheumatoid Arthritis (RA) has been estimated as the most commonly occurring inflammatory arthritis, affecting approximately 0.5-1.0% of the world population [73] and TNF- α overexpression has likewise been present in its bearers. Some follow up studies in TNF- α transgenics, accomplished in the nineties, have found its over-expression in the absence of active T and B cells in patients with this disease [74]. Later on, they have found that there is no requirement for soluble TNF- α to be present, but that the full expression of arthritis may occur even with a membrane-bound form of it (mTNF- α) [75]. In cultures accomplished from synovial cells from bearers of rheumatoid arthritis, the blockage of TNF- α with antibodies reduced the production of IL-1, IL-6, IL-8, and GM-CSF significantly.

8. TUMOR NECROSIS FACTOR ALPHA AND INFLAMMATORY BOWEL DISEASES

Inflammatory Bowel Diseases (IBD) are described in the literature as complex disorders comprised by Crohn's Disease (CD) as well as Ulcerative Colitis (UC) [76]. In such pathologies, TNF- α has been pointed as inflict increased immune activations, not to mention the well-known effects of cytokines as whole, such as fever induction, bone resorption, insulin resistance, anemia and are some of the activities related to this pro-inflammatory cytokine [77, 78]. IBD approach underwent a major revolution when new classes of monoclonal antibodies, such as anti-tumor necrosis factor TNF- α agents, were described [79 - 81]. New drug development focused on TNF- α inhibition has been developed to treat autoimmune affections, such as infliximab and azathioprine, or combination therapy for Crohn's disease. The blocking of TNF- α has been proved efficient in both induction and maintenance of clinical response and remission of IBD [82 - 85]. Table 2 exemplifies the main effects on the pathologies mentioned above.

Table 2. Main effects of TNF- α on the pathologies of this paper.

Pathology	Effects
Periapical Lesions	Stimulates bone resorption
Cardiac injuries	Amplifies Inflammatory response
Arboviruses	Alters vascular endothelial cells causing bleeding
Alzheimer's disease	Modulates Neuroinflammation in Central Nervous system
Cancer	Inhibits tumor growth in general
Reumathoid arthritis	Intensifies IL-1; IL-6; IL-8 and GM-CSF production
Bowel diseases	Increases immune activation, induces fever and anemia

CONCLUSION

Due to its pro-inflammatory effects, TNF- α is directly involved in most of the inflammatory processes in the mammalian organism. It modulates the course of many pathologies with some contradictory effects, either inhibiting or stimulating inflammatory vascular events mainly. Although its interactions with interleukins has been extensively studied, its most complex interactions, however, need to be more investigated.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

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