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The Role of TNFα in Diverse Pathological Processes – Literature Review

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Abstract

Background: TNFα 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. Objective: The aim of this work was to accomplish a literature review concerning the main pathologies that have TNFα as a modulating agent in other to bring light to the main interactions present in the inflammation installed. Methodology of Research: the review was made using the following electronic databases: PUBMED Central, BVS/BIREME, Web of Science, Science Direct, Higher Level Personnel Improvement Coordinator (CAPES) Periodic Portal , The Cochrane Library and PROSPERO. Results: The articles collected showed the role of TNFα in many pathologies, such as Alzheimer's disease, cancer, psoriasis, myocardial infarction, arboviruses, arthritis, Inflammatory bowel diseases, irreversible pulpitis, periodontitis Conclusions: This review concludes that TNFα plays a very significant role in inflammation processes in mammalian organisms. It modulates the course of many pathologies, intensifying or changing the kind of immunological response, depending on the pathology in question. TNFα 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 TNFα 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.

1. Introduction

All cells receive and respond to signals from their surroundings, allowing cell communication. Mating between yeast cells, for instance, is signaled by peptides that are secreted by one cell and bind to receptors on the surface of another. Nevertheless, it is in multicellular organisms that such communication way reaches its highest level of sophistication, for the fact that the cells in these animals and plants have to be regulated to meet the needs of the organism as a whole. This is accomplished by a variety of signaling molecules that are secreted or expressed on the surface of one cell and bind to receptors expressed by other cells, thereby integrating and coordinating the functions of many individual cells that make up organisms as complex as human beings [1].

The binding of most signaling molecules to their receptors initiates a series of intracellular reactions that regulate virtually all aspects of cell behavior, including metabolism, movement, proliferation and differentiation. Understanding the molecular mechanism responsible for such pathways has become a major area of active research. More interesting yet is the fact that most cancers arise as a result of a breakdown in the signaling pathways that control normal cell growth and differentiation, and this unbalance generates defective inductions and proliferation, leading to illnesses. Conversely, many of our current insights into cell signaling mechanisms have come from the study of cancer cells; a striking example of fruitful interplay between medicine and basic research cell and molecular biology [2].

The appropriate immune response depends on the balanced cell-to-cell communication, depending on the conditions of the host organisms as a whole, including nutrition and organic conditions, as well as genetic programming. Cell recruitment and arrival on the inflamed sites is partially obtained by the synchronized synthesis and function of the so-called cytokines and their action on their counterparts: the receptors located mainly on the cell

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membrane; without which the they would never respond promptly. In fact, cytokines define the subpopulation that will be recruited in each step of the immune responses, stimulating recruitment or inhibiting production and release.

The cytokine family is vast, and the way they act *in vivo* still challanges scientists. Their most known members include the Interleukins (IL), Interferon (IFN), Tumor Necrosis Factor (TNF), Coloning-stimulating Factor (CSF), Chemokines (CKs), and Growth Factor (GF) [3]. The name chemokines is derived from chemoattractant cytokines, and is related to their capacity of inducing directed chemotaxis in nearby responsive cells. Among them, Tumor Necrosis Factor alpha has been studied for years and exhaustedly described in the scientific literature [3]. The aim of this work was to accomplish a literature review concerning the main pathologies that have been described in the literature concerning TNFα as a modulating agent.

2. Methodology of the Research

The data collected by this research was accomplished in the following electronic databases: PUBMED Central, BVS/BIREME, Web of Science, Science Direct, Higher Level Personnel Improvement Coordinator (CAPES) Periodic Portal, The Cochrane Library and PROSPERO. The search collected 60 articles which were scrutinized and summarized and finally converted into text.

3. Literature Review

Tumor Necrosis Factor alpha (TNF-α) is a cytokine that acts primarily on the acute phase reaction of inflammation. It has been extensively studied and the use of new approaches in molecular biology has made it possible to identify several polymorphisms in the promoter region of this gene. It is believed that such polymorphisms lead to the differential function of this gene and to the regulation of its production as a cytokine that plays a fundamental role in the inflammatory mechanism, to be explained. TNF-α is mainly produced by macrophages, although they can also be produced by Natural Killer cells (NKs), polymorphonuclear neutrophils (PMNs), mast cells, eosinophils and neurons as well [4]. It is produced and released in the inflammatory processes, playing a significant role in the initiation and coordination of cellular events, which are the response of the immune system to infections [5]. Such characteristics have made this cytokine known as a proinflammatory substance, for showing pyrogenic induction and therefore able to stimulate the onset of fever and apoptosis, inflammation, inhibition of tumorigenesis and viral replication, as well as to respond to infections via activation of IL-1 and IL6-producing cells.

Changes in the regulation of TNF-α have been related to a wide variety of human diseases, such as Alzheimer's disease [4], cancer [6], and psoriasis [7]. Its biological main effects potentialize T and B leukocytes activation, which also affects via feedback chemotaxis, the macrophages and natural killer (NK) cells, which are Antigen Presenting Cells (APC) belonging to the first defensive line of the immunological system: 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. TNF-α also triggers prostaglandins (PG) production, which increases 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 shown that TNFα, in association with other interleukins, potentiate bone resorption capacity [9, 10].

TNF-α has been associated to a vast number of pathologies for decades, simply because its action does not encounter barriers, for being able to reach cell receptors wherever blood irrigates. Therefore, TNF-α has been related to cardiac injury, although its action in most cardiac cell type is still unclear. Anyhow, TNF-α-activated signal transduction pathways have been postulated to play a pertinent role to adverse ventricular remodeling after myocardial infarction, as well as being a major contributor during the development and progression of heart failure [11, 12].

Not until 1975 was TNF-α identified as a soluble factor that caused necrosis of tumors, and thereafter came its designation [13]. It has also 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) [14-17].

In order to play its cellular role, TNF-α can bind to two main receptors namely: TNF receptor 1 (TNF-R1), (55-kDa) and receptor 2 (TNF-R2), (75-kDa), [18-21], which are distinct, but expressed in many different cell lineage surfaces. TNF-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, TNF-R2, is initially expressed intensively by T cells and endothelial cells, for rapid and efficient response by recruiting or inhibiting specific cell types when necessary [22-24]. The former is activated by either sTNF-α or tmTNF-α; while the latter is preferentially activated by tmTNF-α [25, 26].

Sometimes, however, a small degree of overlap and cross talk between both receptors may happen, despite of their 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 NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells), regulating cytokine production, and mediating inflammation and apoptosis, depending on the immunological need [19, 21, 27-29].

Increased levels of TNF-α have been detected in blood serum of patients with heart attack, directly proportional with the severity of the failure. This has made TNF-α implicated as a mediator of cardiac disease pathogenesis, with its serum levels as predictors of this disease. In fact, its overproduction accomplished by cardiac myocytes itself is enough to cause pathological cellular and vascular changes in the myocardium consistent with heart failure [20].

Arboviruses have also been researched in relation with TNF-α alterations. Increased levels of TNF-a have been associated with Dengue virus (DENV) infection. The main symptoms of DENV infection is dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) [18]. It is known that TNF-a 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 [30]. 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 [31].

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 neuroinflammation, but TNF-a 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 if this cytokine is significantly higher in blood [14] and central nervous system [32] of patients with Alheimer 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 [33].

TNFα overexpression has been present in patients with arthritis. Some follow up studies in TNFα transgenics, accomplished in the nineties, have found its over-expression in the absence of active T and B cells in patients with this disease [34]. Later on, they have found that there is no requirement for soluble TNFα to be present, but that the full expression of arthritis may occur even with a membrane-bound form of it (mTNFα) [35].

TNFα is highly involved in patients with cancer. Its effect on the tumorous cells seems to be the formation of oxygen radicals inside the cells exposed to it Zimmerman, *et al.* [36]. 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 TNFα 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 [37], and therefore, the systemic administration of TNFα began to be applied. However, severe toxicity was reported. It seems that humans tolerate a maximum of 8-10μg kg^{-1} body weight of systemically administered TNF-a before life-threatening toxicities set in. Tumor regression on the other hand, demands doses of nearly 400 μg kg^{-1}, making it impossible for clinical use [38-40].

Still concerning cancer, some studies do reveal that the ectopic expression of TNFα at the site of malignancy induces strong and long-term tumor regression [41, 42]. On the other hand, a "dark side" of this cytokine has raised in apparent contradiction to its name. There has been increasingly evidence that, especially in middle and old age, TNFα 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 [43].

Inflammatory bowel diseases (IBD) are described in the literature as complex disorders comprised by Crohn's disease (CD) as well as ulcerative colitis (UC) [44]. In such pathologies, TNFα has been pointed as to 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 [45, 46]. IBD approach underwent a major revolution when new classes of monoclonal antibodies, such as anti tumor necrosis factor TNFα agents, were described [47-49]. New drug development focused on TNFα inhibition has been developed to treat autoimmune affections, such as infliximab and azathioprine, or combination therapy for Crohn's disease. The blocking of TNFα has been proved efficient in both induction and maintenance of clinical response and remission of IBD [50-53].

Dental pathologies have also been related to TNFα serum levels. Upregulation of TNF-α has been discovered in pulpal tissues from teeth with irreversible pulpitis [54, 55]. Two studies have brought light to the role of TNFα in the pulpal tissues. The upregulation of TNF-α has been detected in pulpal tissues from teeth with irreversible pulpitis [54, 55]. The levels were obtained from exudates of teeth with apical periodontitis [56]. TNFα not only has proinflammatory characteristics, as it also seems to act directly on nociceptive neurons, thus increasing pain sensitivity, TNFR1 and TNFR2 were found on nociceptive neurons which transmit peripheral pain to the central nervous system [57], an inevitable outcome from the inflamed pulp. Researchers have also tried subcutaneous injection of recombinant TNF-α, promoting mechanical allodynia through sensitization of C-fiber nociceptors [58], while the application of TNF-α to cultured dorsal root ganglion neurons seem to modulate ion channel activity [59].

Psoriasis is a chronic, genetic, systemic inflammatory pathology characterized by elevated itchy plaques with raised red skin covered with thick silvery scales. It usually affects the elbows, knees, and scalp but can many times affect the legs, trunk, and nails, affecting virtually 1-3% of the general population, and is also responsible to multiple biochemical, immunological, and vascular abnormalities [60]. During the last several years, TNFα antagonists have become first choice for the treatment of moderate-to-severe psoriasis being highly effective for the treatment of both psoriasis and psoriatic arthritis. They also seem to reduce the risk of cardiovascular events in patients with systemic chronic inflammatory disorders. The three TNFα main antagonists most used are infliximab (Remicade®), etanercept (Enbrel®), and adalimumab (Humira®). Although all of them are able to block TNFα *in vivo*, and have been used systematically for the treatment of psoriasis [61].

4. Results

It is expectable that inflammatory diseases be modulated by TNFα due to its being a potent proinflammatory cytokine. Therefore, the articles collected in this research showed that it plays significant roles in many pathologies, such as Alzheimer's disease, cancer, psoriasis, myocardial infarction, arboviruses, arthritis, inflammatory bowel diseases, irreversible pulpitis and periodontitis.

5. Discussion

A real definition of inflammation is complicated due to complexity of the process and the mediators involved in its establishment and development. In this context, TNFα is involved directly or indirectly, modulating the inflammatory response in most, if not in all of the pathological entities.

TNFα as a proinflammatory cytokine enhances the emigration of neutrofilic leukocytes through the walls of the blood vessels right into the adjacent tissues, representing the main cellular phase of inflammation, called diapedesis. Some of these neutrophils seem to move on the inner surface of the endothelium by ameboid motion, putting out pseudopodia, preparing to migrating. Such leukocyte mobilization stimulates the macrophages and NK cells, the most important sort of TNFα producers [4].

Practically, any type of tissue injury evokes an initial accumulation of neutrophilic leukocytes, establishing the cardinal signs of inflammation, enunciated by Celsus, which includes redness, swelling, heat and pain, and all of these signs may be altered by TNFα for being able to influence prostaglandin production and the release of cytokines and chemokines, modulating the vascular changes that will alter blood inflow and outflow. Therefore, it is only expectable that TNFα be able to also modulate pain, since it acts on the nociceptive neurons, whose membranes possess its receptors. TNFα ability to modulate vascular permeability is in direct relationship with PGs, more specifically when it stimulates the upregulation of the acute inflammation phase proteins, such as CRP. The resulting altered permeability implies in increased risk of bleeding when arboviruses pathologies are installed in the human organism, associated with the [8, 31].

One of the most important facts that the study of TNFα has offered to science is its use as a predictor of cardiac diseases when associated with heightened levels of LDL cholesterol and cardiac disease history, as well as its use as a helper in the diagnosis of cancer, whose levels of TNFα are significantly increased. The study of its effects on the vascular endothelial cells gradually made it apparent that the permeability response in inflammation had a complex pattern, probably with a corresponding complexity of the underlying mechanisms influenced by this cytokine.

6. Conclusions

TNFα is 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. Its most complex interactions, however, need to be more investigated in order to better comprehend its effects as a whole.

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