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Pentraxin-3: An acute phase protein as a biomarker

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Abstract
Acute phase proteins are the substances that react the earliest with chemotactic excitations of cytokines in infectious conditions. They also play a role as an acute phase response as part of innate immunity. Acute phase proteins can be used as biomarkers of systemic inflammatory conditions caused by infection/inflammatory responses, regardless of the causative agent. It can also help in the early detection and prognosis of inflammatory responses. Pentraxin-3 is an acute phase protein belonging to the pentraxin family that plays an important role in the defense of living things against pathogens. It is a possible biomarker for the diagnosis and prognosis of infectious and non-infectious diseases, especially those associated with inflammatory processes, involved in cellular and humoral immune response. Its use Its use in both human and veterinary medicine is expanding.

Keywords: *Acute phase protein, inflammation, cytokine, immune response*

1. INTRODUCTION

An inflammatory response occurs when a living organism encounters external agents identified as foreign or when its own cells undergo changes that render them foreign. With the onset of inflammation, the normally inactive complement system is activated, triggering a cascade of biological responses.[1] Cytokines play a crucial role in orchestrating this inflammatory response and ensuring its recognition throughout the organism. The primary cytokines involved in this process include interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), tumor necrosis factor-alpha (TNF-α), and interferon-gamma (IFN-γ).[2]

Cytokines induce the release of pentraxins, which are classified as acute-phase proteins. Based on their structural properties, pentraxins are categorized into short and long pentraxins. Short pentraxins include C-reactive protein (CRP) and serum amyloid P (SAP), while long pentraxins comprise neuronal pentraxin-1 (NPTX-1), neuronal pentraxin-2 (NPTX-2), neuronal pentraxin receptor (NPTX-R), pentraxin-3 (PTX-3), and pentraxin-4 (PTX-4).[1]

Pentraxin-3 (PTX-3), known as an acute-phase protein, is rapidly released in response to inflammatory reactions triggered by tissue damage caused by various factors such as infection, immunological reactions, neoplasia, and trauma.[4,5]

In veterinary medicine, acute-phase proteins, whose plasma levels change rapidly due to infection, inflammation, and trauma, are used for disease diagnosis and prognosis.[5] In recent years, the elevation of plasma PTX-3 levels as a result of the inflammatory response and the strong correlation between plasma PTX-3 levels and severe disease conditions have led to increased research in this field. These findings suggest that PTX-3 could serve as a biomarker for determining disease severity and prognosis.[7] This review is intended to provide a concise overview of the latest advancements pertaining to pentraxin-3.

2. ACUTE PHASE PROTEINS

Acute-phase proteins are synthesized primarily in the liver, as well as in various other tissues and cells, with most of them being glycoproteins. Their secretion is regulated by pro-inflammatory cytokines. They are synthesized in response to the inflammatory reaction occurring at the site of tissue damage, and their plasma levels increase rapidly. Due to their concentration changes following infection, inflammation, and trauma, acute-phase proteins can be used in disease diagnosis and prognosis.[5]

2.1. Pentraxins

Pentraxins are multifunctional pattern recognition molecules (PRMs) that contain an eight-amino acid sequence located in the carboxy-terminal (C-terminal) region. The pentraxin family is classified into short and long pentraxins based on their primary protein structure. The main members of this family include C-reactive protein (CRP), serum amyloid P component (SAP), and pentraxin-3 (PTX-3).[7] Neuronal pentraxins are glycoproteins produced by the NPTXR gene in humans.[1]

Recent studies have reported that plasma pentraxin-3 (PTX-3) levels rapidly increase in response to inflammatory reactions caused by diseases, including infections, autoimmune disorders, and degenerative diseases. The identification of a positive correlation between elevated circulating PTX-3 levels and disease severity in critical

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conditions suggests that PTX-3 could serve as a biomarker for disease assessment.[2]

2.2. Pentraxin-3

Pentraxin-3 (PTX-3) is an acute-phase plasma protein that plays a role in both acute and chronic inflammation as well as innate immunity. PTX-3 is also known as tumor necrosis factor (TNF)-inducible gene 14 protein.[4] PTX-3 can activate all three pathways of the complement system the classical, alternative, and lectin pathways—and can function as a chemotactic factor for various inflammatory cells.[1,4]

2.3. Locations in Which the Synthesisof Pentraxin-3 Occur

The primary source of PTX-3 is myeloid dendritic cells. Additionally, it is produced by fibroblasts, endothelial cells, monocytes, neutrophils, macrophages, smooth muscle cells, renal epithelial cells, synovial cells, chondrocytes, adipocytes, and alveolar epithelial cells. However, PTX-3 production has not been observed in T and B lymphocytes.[2] The production of PTX-3 is regulated by cytokines such as IL-1, IL-8, IL-10, TNF-α, and interferon-gamma (IFN-γ).[9]

2.4. Differences Between Short and Long Pentraxins

Both short and long pentraxins are acute-phase proteins that play an active role in innate immunity and inflammation. The functions, structures, and binding sites of these proteins were defined. While short and long pentraxins share homology in their C-terminal regions, no homology has been observed in their N-terminal binding regions.[9] Unlike short pentraxins, long pentraxins do not exhibit a restricted expression pattern in the liver but are expressed in a much broader range of tissues.[10]

Short pentraxins, such as CRP and SAP, can be stimulated by IL-6, whereas PTX-3 secretion is not induced by IL-6. Instead, PTX-3 is primarily induced by cytokines such as IL-1β, IL-10, and TNF-α in various tissue cells, including myeloid cells, epithelial cells, endothelial cells, and fibroblasts.[8] Although IL-6 plays a role in inflammation, it does not stimulate PTX-3 synthesis.[4]

PTX-3 differs from CRP and SAP in terms of gene organization, chromosomal location, synthesis sites, inducing stimuli, and binding regions. Unlike CRP and SAP, PTX-3 can activate all three pathways of the complement system: the classical, alternative, and lectin pathways.[1]

In human studies, plasma PTX-3 has been identified as an early-induced gene. A positive correlation has been observed between plasma PTX-3 levels and disease severity, and the increase in plasma PTX-3 levels has been found to occur more rapidly than that of CRP (11). Polymorphonuclear leukocytes (PMNs) serve as a ready-to-release reservoir of mature PTX-3 in response to microbial recognition or tissue damage. Vascular endothelial cells (ECs) are also a significant source of PTX-3 in response to inflammatory signals. Additionally, IL-10 and bacterial lipopolysaccharides (LPS) induce PTX-3 expression.[12]

2.5. Complement System Activation by Pentraxin-3

The complement system is composed of plasma proteins that play crucial roles in host defense and the regulation of inflammatory processes. PTX-3 activates all three pathways of the complement system: the classical, alternative, and lectin pathways.[1] As an acute-phase protein, PTX-3 recognizes a wide range of microorganisms, including fungi, bacteria, and viruses, and triggers antimicrobial mechanisms. Its interaction with P-selectin plays an immunoregulatory role in inflammation by modulating neutrophil release and complement system activation.[13]

Complement component-1q (C1q) is the first identified binding site for PTX-3 and facilitates the activation of the classical pathway.[14] Unlike short pentraxins, PTX-3 binding to C1q does not require prior aggregation of the protein or the presence of calcium ions.[15] The binding of PTX-3 to C1q leads to the accumulation of complement component-3 (C3) and complement component-4 (C4), thereby activating the classical pathway of the complement system.[16] Additionally, PTX-3 interacts with members of the lectin pathway, such as ficolin-1, ficolin-2, and mannose-binding lectin (MBL), thereby activating the lectin pathway. Furthermore, in addition to the classical and lectin pathways, PTX-3 interacts with factor H and complement component-4 binding protein (C4BP), leading to the activation of the alternative pathway.[1]

There are two specific binding sites on factor H that allow PTX-3 to attach. Through this mechanism, PTX-3 helps regulate excessive inflammatory responses by binding to factor H, thereby controlling alternative pathway activation, preventing tissue damage, and enhancing the accumulation of opsonic molecules.[17]

PTX-3 plays a key role in the immune response of the complement system by interacting with three key complement components: C1q, ficolin-2, and factor H. PTX-3 promotes the deposition of factor H and C3b on apoptotic cells, facilitating the fusion of the cell membrane with neutrophil granules during apoptosis. Granules on the surface of apoptotic cells lead to PTX-3 translocation. The increased PTX-3 concentration in apoptotic vacuoles enhances the recognition and phagocytosis of apoptotic neutrophils by macrophages. PTX-3 is released in response to proinflammatory signals and prevents the initiation of an immune response against autoantigens by capturing dying cells during the inflammatory process. Additionally, it accelerates the phagocytosis of late apoptotic neutrophils.[2]

2.6. Pentraxin-3 and Inflammation

Inflammation is the response of living tissue to any foreign biological or non-biological agent, endogenous or exogenous tissue damage, harmful pathogens, and their remnants. Its primary function is to neutralize or eliminate these agents or regenerate tissue for repair purposes. In short, inflammation is the reaction of vascularized tissue to various microorganisms.[11] The relationship between inflammatory cells and PTX-3 is crucial, as neutrophils contain PTX-3, which is synthesized during cell maturation and stored at high levels in granules. Together with other inflammatory cells, neutrophils become activated during inflammation and release PTX-3 from their granules.[4] Neutrophils serve as a "ready-to-use" protein reservoir for PTX-3, which is released

in response to microbial recognition and inflammatory signals.[16]

The primary proinflammatory cytokines involved in PTX-3 expression and the initiation of the inflammatory response are TNF-α and IL-1β.[18] These key inflammatory mediators, along with Toll-like receptor (TLR) ligands and microbial products such as lipopolysaccharides (LPS), lipoarabinomannans, and outer membrane proteins, can stimulate PTX-3 production.[19] PTX-3 is locally synthesized at sites of inflammation by various cell types, including vascular endothelial cells and smooth muscle cells (SMCs), in response to different inflammatory stimuli and microbial components. Its production is induced by IL-1β, LPS, and oxidized low-density lipoproteins. Additionally, PTX-3 expression in monocytes is triggered by IL-1β, LPS, and TNF-α.[11]

Studies in humans and mice have demonstrated that PTX-3 acts as an acute-phase protein. Under normal conditions, plasma PTX-3 levels are below 2 ng/mL, but in cases of toxicosis, sepsis, and other inflammatory or infectious conditions, these levels can rapidly increase to 200–800 ng/mL within 6–8 hours. Significant elevations in PTX-3 levels have also been observed in sepsis, septic shock, tuberculosis, dengue virus, and meningococcal infections. Furthermore, a strong correlation has been identified between plasma PTX-3 levels and disease severity in these cases.[11]

Experimental studies on PTX-3-deficient guinea pigs have shown that IL-1-mediated neuronal damage is more extensive and severe in the absence of PTX-3. It has been observed that PTX-3 irreversibly binds to damaged neurons, thereby protecting them from injury. As a result, PTX-3 is thought to contribute to resistance against neurodegeneration.[2]

2.7. The Role of Pentraxin-3 in Inflammation

When exogenous PTX-3 is administered or endogenous PTX-3 is released, a negative feedback mechanism in hematopoietic cells is activated. By binding to P-selectin, PTX-3 helps prevent excessive neutrophil release. PTX-3 is secreted by activated lymphocytes, thereby suppressing neutrophil release and contributing to the regulation of inflammation. Additionally, PTX-3 regulates inflammation by inhibiting the glycosylation-dependent regulatory effect of antibodies. Glucocorticoid hormones assist in regulating PTX-3 expression through a cell-dependent pathway and enhance PTX-3 release from fibroblasts and endothelial cells. In vivo glucocorticoid administration has been shown to increase PTX-3 levels, and elevated circulating PTX-3 levels have been observed in patients with Cushing's syndrome.[2]

Unlike the classical and lectin pathways, the alternative pathway (AP) is spontaneously activated. It recognizes complement component 3b (C3b) molecules on host cell surfaces and is rapidly inactivated, whereas C3b molecules accumulating on foreign cells and particles remain active, leading to rapid amplification of AP activation. Healthy cells are protected from AP activation by factor H (FH), the main AP regulator in plasma and other body fluids. This protective mechanism is based on the recognition of C3b on host cells. Factor H prevents the inactivation of C3b molecules on host cell surfaces, thereby inhibiting further AP activation on undamaged cells.[20]

2.8. The Role of Pentraxin-3 in Sepsis

In the early stages of inflammation, PTX-3 recognizes microbial fragments, activates the classical complement pathway, and facilitates antigen recognition by macrophages and dendritic cells. When systemic PTX-3 concentrations are evaluated, persistently high PTX-3 concentrations have been observed in deceased patients, suggesting that PTX-3 could be a potential biomarker for identifying high-risk patients. Elevated plasma PTX-3 levels from the first day of sepsis may be associated with increased mortality. PTX-3 is also linked to coagulation/fibrinolysis dysfunction associated with sepsis. The concentration of PTX-3 in the blood is usually low under normal conditions (< 2 ng/ml in humans), but it can rise rapidly during septic conditions, endotoxemia and other SIRS events. In a study conducted on 537 patients brought to the emergency department, patients were grouped as follows. Group 1 (no SIRS, no bacterial infection), group 2 (no SIRS, there is a bacterial infection), group 3 (with SIRS, there is a bacterial infection), group 4 (there is sepsis) and group 5 (there is severe sepsis). The mean PTX-3 concentrations were measured as 2.6; 4.4; 5.0; 6.1 and 16.7 ng/ml, respectively. The diagnostic threshold values for PTX-3 in humans as ≥ 5.0 ng/mL for sepsis and ≥ 9.0 ng/mL for septic shock was identified.[21]

2.9. The Role of Pentraxin-3 in Viral Infections

A study by Foo et al.[12] investigated whether Pentraxin-3 (PTX-3) plays a protective role in host defense against viral infections by examining its function in infections caused by Alphavirus. The researchers identified PTX-3 as an immunoregulatory molecule. They observed that immune cells, particularly neutrophils and monocytes, accumulated at the site of infection and that neutrophils expressed PTX-3. The monocytes at the infection site differentiated into phagocytic dendritic cells and macrophages, forming PTX-3-RRV complexes. These complexes interacted with PTX-3 receptors, facilitating endocytosis into the cytoplasm. The PTX-3-RRV complex was recognized by pathogen receptors, enhancing viral entry into the cytoplasm. This process activated the NF-kB pathway, stimulating the production of pro-inflammatory cytokines, particularly TNF-α, thereby strengthening the immune response and triggering an early immune response.[13] In another study, Reading et al.[21] investigated the effects of PTX-3 on influenza virus infection in humans. Their findings indicated that PTX-3 neutralized viral infectivity through its sialic acid component, thereby reducing both viral load and mortality.[22]

2.10. The Role of Pentraxin-3 in Bacterial Infections

Xu et al.[22] conducted a study to evaluate the antibacterial effects of porcine PTX-3 against *Streptococcus suis* type 2 infection. In an in vitro antibacterial assay, the bacterial growth curve changed when PTX-3 acute-phase protein was added to the liquid medium of various bacterial species. As PTX-3 concentration increased, bacterial growth rate slowed, and the plateau phase was significantly delayed. The study concluded that the antibacterial effect of PTX-3 on bacterial proliferation was

dose-dependent. Furthermore, the researchers found that PTX-3 enhanced the phagocytic activity of primary porcine macrophages and suggested that porcine PTX-3 might play a role in bacterial opsonization.[23]

2.11. The Role of Pentraxin-3 in Fungal Infections

In fungal infections, PTX-3 is stored in neutrophil granules and rapidly released upon cell stimulation. PTX-3 can opsonize fungi such as *Aspergillus fumigatus* conidia within host cells. In neutrophils deficient in PTX-3, fungal recognition and clearance were found to be less effective. PTX-3 interacts with lectins on the surface of pathogens such as *Aspergillus* and *Candida*, promoting complement accumulation and inducing PTX-3 expression in macrophages through zymogens.[13]

3. PENTRAXIN-3 IN HUMAN MEDICINE

3.1. Cardiovascular Diseases and Pentraxin-3

PTX-3 has been identified as a potential biomarker for cardiovascular diseases, exhibiting cardioprotective and atheroprotective roles. Studies have shown that plasma PTX-3 levels rapidly rise in acute myocardial infarction (AMI) and heart failure, reflecting the extent of tissue damage and potentially predicting the risk of mortality.[12] It has been reported that plasma PTX-3 is not influenced by coronary risk factors such as cholesterol, high-density lipoprotein (HDL), hemoglobin A1C, smoking, gender, and obesity.[24]

PTX-3 is described to play a dual role in systemic inflammation. Increased levels of IL-1β and TNF-α exert pro-inflammatory effects on the vascular layer, which intensify vascular damage through the release of neutrophil granules and reactive oxygen species. Conversely, PTX-3 reduces TNF-α-activated NF-kB signaling by lowering the levels of monocyte chemoattractant protein-1 (MCP-1), which is essential for macrophage migration and infiltration, thereby offering a protective role in vascular damage. Additionally, PTX-3 decreases the levels of HLA-DR and CD86, which contributes to vascular protection.[4,12]

In cardiac and inflammatory reactions, elevated PTX-3 expression in the myocardium has been observed. This is due to the production of PTX-3 by vascular cells in response to inflammatory signals and the formation of oxidized low-density lipoprotein (oxLDL) in atherosclerotic lesions. Studies on PTX-3 levels in acute myocardial infarctions (AMI) have emerged as a result. Additionally, PTX-3 expression has been found to be more abundant in leukocytes and adipose tissue in patients with high oxLDL levels due to atherosclerosis.12 Research indicates that PTX-3 peaks in plasma 6-8 hours after symptom onset and does not correlate with C-reactive protein (CRP).[24] Studies have shown that plasma PTX-3 levels increase within approximately 3.2 hours in patients diagnosed with AMI, peak at 7.5 hours, and return to baseline levels within 3 days. In patients diagnosed with myocardial infarction (MI), plasma PTX-3 concentration values were measured at >3.1 ng/ml, and in AMI patients, values were >10.73 ng/ml.24, 25, 26, 28 In patients diagnosed with cardiac arrest, CRP was found to have lower accuracy than PTX-3 in predicting the development of Multiple Organ Dysfunction Syndrome (MODS). In a prospective study involving heart failure patients with normal ejection fraction, despite BNP levels remaining within normal reference ranges, PTX-3 values were measured as elevated. The study concluded that PTX-3 is a more useful biomarker for predicting disease prognosis and evaluating clinical outcomes compared to BNP.[12,24]

3.2. Ischemia and Reperfusion Injury and Pentraxin-3

In ischemia and reperfusion injury (IRI), PTX-3 concentrations have been measured to be elevated in proportion to the extent of the damage. To reduce high neutrophil levels to baseline values and evaluate the role of PTX-3 in regulating the severity of inflammation, PTX-3 was administered to patients. At the end of the treatment, it was found that PTX-3 reduced local edema formation and regulated inflammation by decreasing neutrophil-endothelial cell interactions, resulting in an encouragingly favorable prognosis. This feature of PTX-3 has been described in brain, heart, lung, and renal ischemia-reperfusion injuries. However, some studies have suggested that PTX-3 regulates inflammation in intestinal IRI, while others proposed an opposite role.[29]

3.3. Pulmonary Diseases and Pentraxin-3

Pentraxin-3 acts as an acute-phase protein responsible for innate immunity in the lungs. IL-1, the most well-known cytokine responsible for lung inflammation, is mediated by PTX-3 in inflammation associated with lung damage. By activating inflammatory cells in endothelial cells, PTX-3 plays a role in regulating adhesion molecules, and its direct effects include bronchoconstriction, vasoconstriction, edema, neutrophil chemotaxis, and mucus production. IL-8 is the most important chemotactic factor in the lungs; hypoxia, hyperoxia, and endotoxins stimulate IL-8 production, thereby increasing the levels of pro-inflammatory cytokines. In terms of tissue response, the high levels of PTX-3, especially during the acute phase, suggest that it could serve as an early biomarker for the severity and prognosis of the disease. Experimental studies have shown that excessive PTX-3 release in response to lung inflammation is directly correlated with mortality.2 Studies have found that PTX-3 levels peak in the early time frame, remain high on the 2nd and 5th days in non-surviving patients, and decrease after the 1st day in surviving patients.[2, 25, 30]

3.4. Renal and Urinary Tract Infection Diseases and Pentraxin-3

Many kidney diseases are characterized by the influx of monocytes and T lymphocytes into the tubulointerstitium. These infiltrating cells contribute to the renal inflammatory response by releasing inflammatory mediators such as IL-1 and TNF-α, thereby activating the resident renal tubular epithelial cells. Several studies have shown that activated tubular epithelial cells produce large amounts of chemokines, cytokines, and complement components. Therefore, tubular epithelial cells play a significant role in renal inflammatory processes, and PTX-3 is expressed during inflammatory reactions in the kidneys.[31]

In urinary tract infections caused by Klebsiella, Enterococcus, Pseudomonas, and Escherichia coli, inflamma-

tory cytokines (IL-1β and TNF-α) and toll-like receptors (TLRs) are induced to trigger PTX-3 secretion from urothelial and renal cells. The primary sources of PTX-3 are leukocytes and urothelial cells. Studies have shown increased PTX-3 expression in urinary tract infections. A lower PTX-3 level after treatment could indicate the absence of infection.[32]

3.5. Meningococcal Infections and Pentraxin-3

Neisseria meningitidis is an acute bacterial disease that can lead to death or result in vision, hearing problems, brain damage, liver and kidney failure, and limb loss within hours. A study conducted on 26 patients, including those who experienced shock and those who did not, measured plasma PTX-3 levels. In patients with shock, PTX-3 levels were found to be 801 µg/L, whereas in those without shock, it was 256 µg/L. This result indicated a significant difference in the peak concentration of PTX-3 between patients with and without shock. PTX-3 peaked within the first hours after ICU admission, while CRP peaked after 48 hours, thus suggesting that PTX-3 is an early marker of shock. Therefore, high PTX-3 and low CRP levels at admission are considered indicators of meningococcal shock. The time difference between the peaks of PTX-3 and CRP suggests that PTX-3 is induced by early pro-inflammatory cytokines like TNF-α and IL-1β, whereas CRP is produced more slowly in the liver under the influence of IL-6.[33]

3.6. Inflammatory Bowel Diseases and Pentraxin-3

Crohn's disease and ulcerative colitis are subclasses of Inflammatory Bowel Diseases (IBD), which are diagnosed through clinical history, physical and laboratory examinations, radiology, endoscopy, and biopsy results. PTX-3 is normally produced by colon cells, and its secretion increases in inflammatory conditions. Since neutrophils play a role in the pathogenesis of these diseases, plasma PTX-3 levels were measured in the blood based on disease subtypes, activities, and involvement. The study found that PTX-3 was not an appropriate biomarker for monitoring Inflammatory Bowel Disease (IBD) and could not distinguish between the two subtypes. In Crohn's disease, PTX-3 was inadequate for indicating the affected area; however, in ulcerative colitis, it could demonstrate the extent of the colon involvement without the need for endoscopic examination. Therefore, plasma PTX-3 levels in ulcerative colitis patients could be monitored between endoscopic checks for prognostic purposes.[34] In active Crohn's disease, IL-6 expression was found to increase, whereas IL-1 was more effective in ulcerative colitis, which subsequently raised plasma PTX-3 levels. Based on these findings, it is believed that PTX-3 could be used for prognosis in patients with inflammatory bowel diseases.[24]

3.7. Pentraxin-3 in Oncology

Pentraxin-3 is known to play a significant role in tissue regeneration as well as in innate immunity and inflammation. Based on several studies, PTX-3 appears to have a dual role in cancer; excessive expression in certain situations has been identified as a negative prognostic marker, while in others, it is considered to have an oncosuppressive role. This dual role of PTX-3 is believed to depend on the type of cancer, the cellular source, and the tumor's microenvironment.[19]

In a study conducted on PTX-3 deficient mice, an increased number of tumor-infiltrating macrophages (TAMs), production of pro-inflammatory cytokines, and an accumulation of C3 and C5a due to excessive activation of the complement system was observed. PTX-3 deficiency also led to reduced Factor H localization, resulting in increased C3 accumulation, which contributed to intensified tissue damage. The study concluded that PTX-3 acts as an extrinsic oncosuppressor capable of controlling inflammation associated with carcinogenesis, but further studies are needed to understand this role more deeply.[35]

4. PENTRAXIN-3 IN VETERINARY MEDICINE

Acute-phase proteins whose concentrations change following infections, inflammation, and trauma in animals can be used for diagnosis or monitoring the course of the disease. Recent studies have reported that the plasma concentrations of acute-phase proteins can be used as biomarkers in the diagnosis, prognosis, and monitoring of diseases.[5,]

4.1. Pentraxin-3 in Calves with Sepsis

Sepsis can be defined as a condition characterized by the development of a systemic inflammatory response syndrome (SIRS) caused by a confirmed or suspected infection, often leading to death and potentially accompanied by systemic organ failure. Since PTX-3 is not affected by IL-6 levels, plasma PTX-3 levels reflect the severity of an infection directly and are less influenced by other concurrent inflammatory conditions, making it valuable in the early diagnosis and monitoring of the disease.[21]

In a study conducted on calves, plasma PTX-3 levels were measured in healthy calves (n=10) at 2.62 ng/ml, in calves with sepsis that survived (n=9) at 3.22 ng/ml, and in calves that died from sepsis (n=11) at 3.39 ng/ml. PTX-3 levels were found to be higher in septic calves compared to healthy calves, demonstrating the potential of PTX-3 as a diagnostic parameter. Although the higher plasma PTX-3 concentrations in deceased calves were not statistically significant, its use as a prognostic indicator may provide valuable insight for future research.[21]

4.2. Pentraxin-3 in Shipping Fever Disease

Shipping Fever disease is characterized by lung inflammation in cattle, caused by *Mannheimia haemolytica*. Chemotactic inflammatory mediators, endothelial cells, neutrophils, and monocytes induce PTX-3 expression, and infection of the lungs with *M. haemolytica* stimulates PTX-3 production in areas of inflammation. PTX-3 recognizes and binds to the pathogen, activates the complement system, and plays a role in the clearance of apoptotic and necrotic cells, thereby contributing to the preservation of lung tissue. In line with the obtained data, alveolar and pulmonary intravascular macrophages and migrating inflammatory cells lead to the local release of PTX-3 from epithelial cells. Alveolar macrophages, as local immune cells, are among those that express PTX-3 in response to bacterial and fungal pat-

hogens. PTX-3 released from neutrophil-specific granules has been observed to bind to P-selectin, reducing the local chemotaxis of neutrophils to the region, thus indicating the protective role of PTX-3 in bacterial lung inflammation. Platelets, which are activated by P-selectin, von Willebrand Factor, and Toll-like receptor 4, promote neutrophil accumulation. The data showing that bovine platelets contain PTX-3 suggest that locally released PTX-3 may reduce neutrophil aggregation, thus affecting vascular inflammation. The study in cattle supports the hypothesis that PTX-3 is expressed in the lungs and that its expression increases in calves' lungs infected with *M. haemolytica*.[36]

4.3. Pentraxin-3 in Bovine Tuberculosis

In a study on bovine tuberculosis, it was found that PTX-3 expression increases during the early stages of the disease and peaks within a short period, after which PTX-3 levels decrease as the disease progresses. In acute inflammation caused by *Mycobacterium bovis*, neutrophils are activated, and previously expressed PTX-3 is released into the extracellular space. Neutrophils serve as a reservoir for the early release and activity of PTX-3 during acute inflammation. The stimulation of PTX-3 release along with inflammation delays the apoptotic death of neutrophils. A prolonged neutrophil lifespan is essential for supporting the host's protection against infection. However, there is a feedback mechanism that prevents excessive inflammation. The study concluded that neutrophils, both in acute and chronic infections, act as the first line of defense against *M. bovis*, recognizing and eliminating the invasive microorganisms.[37]

4.4. Pentraxin-3 in Bovine Respiratory Disease Complex (BRDC)

Infectious bovine respiratory disease complex (BRDC) is one of the most significant herd problems both worldwide and in the country. Due to the multiple risk factors associated with the disease, including environmental factors and management mistakes, it remains a major issue in modern livestock industries. PTX-3, a relatively new biomarker in veterinary medicine, has been studied infrequently in BRDC. A study using bronchoalveolar lavage (BAL) samples from animals diagnosed with BRDC showed that PTX-3 levels were statistically higher than in the control group, especially with the increased lung damage. Townsend and Singh[40] concluded that PTX-3 protects lung tissue during bacterial inflammation. In a study by Akyüz et al.,[41] PTX-3 levels were found to be high in lung tissue exhibiting severe damage. The study concluded that the increased PTX-3 concentrations in inflammation were due to its regulation of the severe inflammation in lung tissue, thereby protecting the lung tissue.[42,43]

4.5. Pentraxin-3 in Recurrent Airway Obstruction in Horses

Recurrent airway obstruction (RAO) is a common cause of chronic respiratory disease in adult horses, often due to exposure to low-quality hay or dusty environments such as stables. The clinical signs of RAO result from lower airway inflammation, which includes bronchospasm, excessive mucus production, and airway hypersensitivity to non-specific stimuli. A study on horses diagnosed with RAO identified cells capable of producing PTX-3 in their airways using immunohistochemistry. PTX-3 was detected in macrophages and young neutrophils from bronchoalveolar lavage fluid (BAL) samples taken from both sick and healthy horses. PTX-3 was also found in equine eosinophils, though its source was unidentified. In RAO-affected horses, the percentage of neutrophils in the BAL was significantly higher (22.94 ± 3.4%) compared to the control group (12 ± 4.71%), and it was determined that macrophages in the BAL cells stimulated the release of PTX-3. It was concluded that TNF-α and IL-1b were excessively expressed in the airways of RAO-affected horses and could serve as pro-inflammatory mediators, contributing to the expression of dust-induced PTX-3 in BAL cells. Additionally, it was concluded that PTX-3 was induced by inflammatory mediators such as LPS and TNF-α, rather than by direct exposure to dust.[38]

4.6. Pentraxin-3 in Feline Parvovirus (FPV) Infection

Feline panleukopenia (FPL) remains a significant problem in the feline population, and as such, there are ongoing studies to investigate all aspects of the disease. In a recent study by Eroğlu and Erdoğan,[44] a significantly elevated serum PTX-3 level (58.69 pg/mL) was observed in feline panleukopenia (FPL) cases, in comparison to healthy cats (where PTX-3 was undetectable). This phenomenon is hypothesised to be a physiological response aimed at mitigating inflammation, tissue damage, and the elimination of infectious agents. The conclusion drawn was that further clinical studies with a large number of infected cats are required in order to clarify these findings and to use PTX-3 as a reliable biomarker in cats infected with FPV.

4.7. Breast Milk and Pentraxin-3

Studies conducted so far have explored PTX-3 as a biomarker in both human breast milk and infants. The average plasma PTX-3 levels were measured as 4.28 ng/ml in children over one year of age, 6.07 ng/ml in infants, and 11.69 ng/ml in neonates. In neonates born via cesarean section, the average plasma PTX-3 level was 13.24 ng/ml, whereas in those born through natural delivery, it was 18.41 ng/ml.[27] Plasma PTX-3 levels were reported as 0.45 ± 0.05 ng/ml in neonates.[39]

In order to assess the in vivo capacity for PTX-3 production and plasma PTX-3 levels in neonates, LPS was injected into newborn and adult mice. Plasma PTX-3 levels were measured at 378.95 ± 15.64 ng/ml in adult mice and 175.86 ± 29.94 ng/ml in neonates. These differences in plasma PTX-3 levels led to the hypothesis that breast milk may compensate for the immune system deficit in neonates. However, based on the plasma PTX-3 measurements, it was concluded that the high plasma PTX-3 levels in the mother were not related to the plasma PTX-3 in the breast milk. Therefore, the production of PTX-3 by mammary tissue and mammary epithelial cells was examined, and it was found that PTX-3 is expressed in the mammary gland and induced by TNF-α and IL-1β. The protective effect of plasma PTX-3 in colostrum was investigated in mice, and it was observed that plasma PTX-3 had a protective effect 24 hours after infection with *Pseudomonas aeruginosa*, though this

effect partly disappeared 48 hours later. As a result, it was concluded that PTX-3 is induced by TNF-α and IL-1β from mammary epithelial cells and found in colostrum, but the long-term protective effect of plasma PTX-3 in colostrum diminished after 48 hours.[39,40]

In our own study conducted on cattle, PTX-3 levels were measured for the first time in colostrum, milk, and calf serum during the neonatal period. On day 0, the PTX-3 concentration in colostrum was measured at 3.53 ± 1.17 ng/ml, while in calf serum, it was 1.19 ± 0.48 ng/ml. The average serum PTX-3 level of calves sampled 24 ± 4 hours after receiving colostrum was 2.56 ng/ml. The results indicated a statistically significant increase in PTX-3 levels between day 0 and day 1 in calf serum, which paralleled the IgG concentration in colostrum. There was also a statistically positive correlation between day 0 serum PTX-3 and colostral IgG, PTX-3, IL-1β, and TNF-α. During the neonatal period, the concentration increase in serum PTX-3, similar to serum IgG, showed a positive correlation with the risk of disease. It was concluded that PTX-3 could be used as a biomarker to predict the occurrence of diseases such as enteritis, omphalitis, pneumonia, and mixed diseases in calves (TUBITAK NO:123O658, not yet published).

5. CONCLUSION

PTX-3 is produced by a variety of cells, including macrophages, neutrophils, dendritic cells, smooth muscle cells, and hepatic cells. Studies have shown that PTX-3 increases in response to inflammation caused by pathogens and can be used as a biomarker. In the early stages of inflammation, PTX-3 recognises microbial components, activates the classical pathway of the complement system, and facilitates antigen recognition by macrophages and dendritic cells. Notably, PTX-3 activates not only the classical pathway but also all three pathways of the complement system. Furthermore, neutrophils function as a "ready-to-use" protein depot for microbial recognition and inflammatory signals in response to PTX-3, enabling PTX-3 to differentiate itself from other acute-phase proteins. Notably, PTX-3 reaches peak levels in plasma within 6-8 hours during the early stages of inflammation.

As PTX-3 levels rapidly increase in the plasma in response to inflammation, in contrast to the behaviour of other acute-phase proteins, and show a positive correlation with severe disease conditions, this has resulted in a significant increase in research activity in this area. Studies have demonstrated that plasma PTX-3 concentrations are closely related to the severity of diseases. While PTX-3 levels are low in animals that recover from infections and diseases, they are high in those that die. Consequently, elevated PTX-3 levels have been identified as a valuable tool in the identification of high-risk patients and the prediction of disease prognosis.

In conclusion, studies suggest that the acute-phase protein PTX-3 may serve as a biomarker for determining the severity, mortality, and prognosis of diseases. Since PTX-3 levels in plasma are less affected by IL-6 levels, they directly reflect the severity of an infection and are less influenced by other concurrent inflammatory conditions, making PTX-3 an important tool for early diagnosis and monitoring of diseases. While the field of veterinary medicine has recently begun to explore the potential of PTX-3 as a diagnostic tool, the research is in its nascent stages and has not yet reached the level of sophistication seen in human medicine. The threshold value for PTX-3 in healthy and diseased animals remains to be delineated, underscoring the need for further research in this area to fully realise the potential of this promising biomarker.

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