

INTERLEUKIN-6 AND ITS IMPERATIVE ROLE IN VARIOUS DISORDERS AND DISEASES

Abstract

The cytokine Interleukin-6 (IL-6), plays an important role in both the pathological process of inflammatory disorders and the maintenance of physiological balance in various tissues across living organisms. Numerous diseases are accompanied with significant increase in IL-6 expression in different tissues. Through this study we tried to study the significance of IL-6 in various disease pathogenesis. For infectious diseases, we highlighted how IL-6 directs the immune response against pathogens, promoting protective immunity or contributing to immunopathology. In the context of autoimmune disorders, we discussed the deregulation of IL-6 and its impact on self-tolerance and the development of autoimmune responses. The understanding of IL-6 in disease contexts has greatly expanded in recent years, enabling the development of targeted therapies to tackle various pathological conditions. This study aims to bring together the current knowledge on IL-6 involvement in various diseases and it gives an insight on potential avenues for future research and therapeutic strategies.

Keywords: Neurological disorders, rheumatoid arthritis and viral infections

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I. INTRODUCTION

Originally known by approximately ten different names, each corresponding to a distinct protein variant, Interleukin 6 (IL-6) possesses a unique history among cytokines due to its accidental cloning long before the discovery of its primary natural function. In an endeavor to clone interferon- β (IFN- β) cDNA from mortal fibroblasts (Weissenbach et al, 1980), researchers unintentionally obtained two identical cDNA copies derived from a 1.3-kb mRNA that responded to poly(rC), poly(rJ), and cycloheximide stimulation. The resulting 26-kd protein was initially labeled as "IFN- β 2," as *Xenopus laevis* oocytes transfected with this mRNA exhibited antiviral activity that could be hindered by antisera against IFN- β . Similarly, adopting a comparable strategy, (Content et al, 1982) cloned the same 1.3-kb mRNA species. However, they determined that the protein, named "26K factor," lacked antiviral activity and lacked serological similarity to IFN- β . Although subsequent sequences released separately by both research groups revealed the absence of structural resemblance to IFN- β , they were unable to definitively resolve the debate surrounding the interferon's functional impact.

Another pathway leading to the emergence of IL-6 was the recognition that activated T cells generate a factor responsible for stimulating B cell differentiation. This factor could induce immunoglobulin (Ig) production in activated B cells or B-cell lines immortalized by Epstein-Barr virus (EBV) infection (Teranishi et al, 1982; Hirano et al, 1984). This particular molecule, initially referred to as B-cell stimulatory factor 2 (BSF-2), was isolated and cloned from a mortal T-cell line transformed by leukemia-type 1 virus (HTLV-1). The observed properties and cellular source of BSF-2 bore no apparent connection to IFN- β 2/32/26K. However, upon the release of the BSF-2 sequence, it was revealed to be the same as that of the factor from fibroblasts.

Thirdly, the investigation that ultimately led to the recognition of IL-6 emerged from the exploration of growth factors associated with plasmacytomas and B-cell hybridomas. Although the presence of such factors had been acknowledged for a considerable period (Metcalf et al, 1975; Corbel et al, 1984), their definitive characterization remained elusive due to the scarcity of stable cell lines dependent on these factors. When these cell lines finally became accessible, along with reliable material sources, it is then followed by the purification of these growth factors. A hybridoma growth factor in mice was isolated from the supernatant of a co-cultured T-cell line. This factor displayed no sequence similarity to known proteins and was initially labeled as IL-HPI. Similarly, plasmacytoma growth factor (PCTGF) was purified from macrophage supernatant. Progress in understanding the human counterparts of these molecules accelerated when it was realized that factor-dependent mouse hybridomas could be employed to guide their purification. This strategy led to the isolation of human hybridoma/plasmacytoma growth factor (HPGF) from medium conditioned by an IL-1-treated osteosarcoma cell line. Remarkably, the N-terminal amino acid sequence of this factor bore limited resemblance to the hybridoma growth factor of mouse but was a precise match for IFN- β 2/32//BSF-2/26K. The complete equivalence between these molecules was confirmed through the independent cloning of hybridoma growth factor of human (Brakenhoff et al, 1987) and the demonstration that showed that recombinant 26K exhibited HPGF activity (Poupart et al, 1987). Establishing the link between the human IL-6 and murine factor proved to be more intricate due to notable differences at the N-terminus. Cloning of cDNA of the mouse protein eventually unveiled how identical it is to the human hybridoma growth factor (Van Snick et al, 1988).

The revelation that IFN- β 2/32, BSF-2, 26K and hybridoma/plasmacytoma growth factor were, in fact, a single entity prompted the suggestion to rename these factors as IL-6. Subsequently, another significant development emerged when researchers uncovered that the action of hepatocyte-stimulating factor, a monocyte-derived protein could be inhibited by anti-IL-6 antibodies. This finding suggested IL-6 involvement in the regulation of the acute phase response. Eventually, the method of expression cloning brought to light two additional aspects of IL-6 functionality: its involvement in hematopoiesis (Ikebuchi et al, 1987) and its role as a factor of differentiation for cytotoxic T cells.

Subsequently, IL-6's involvement has been detected in various processes including tissue regeneration (Corbel et al, 1984; Aarden et al, 1985), inflammation (Van Snick et al, 1987; Nordan et al, 1987) and defense against pathogens (Van Damme et al, 1987). Research has shown that T cells and hematopoietic precursors become receptive to their corresponding growth and differentiation factors when IL-6 is released from damaged or infected tissue. Furthermore, the release of adrenocorticotrophic hormone from the pituitary is triggered, initiation of synthesis of acute phase proteins in the liver occurs, and antibody production is prompted. Considering the swift rise of IL-6 following injury or infection, combined with its widespread production capability in virtually all cells, it becomes evident that this cytokine functions akin to a distress signal.

II. IL-6 AND NEUROLOGICAL DISORDERS

Interleukin-6 (IL-6) holds a vital role in maintaining the balance of neural tissue and causing inflammatory conditions. Various changes in neural health, like those seen in Parkinson's, Multiple sclerosis (MS), , and Alzheimer's disease, are linked to increased IL-6 levels within the brain. Patients with disrupted sleep patterns often show higher levels of IL-6 at night, while the lack of IL-6 in mice causes them the tendency to spend more time in sleep with rapid eye movement associated with dreaming. IL-6 plays a key role in repair of peripheral nerves, the development of oligodendrocytes and acts as a growth factor for neural cells.

Physiologically, the brain contains minimal levels of IL-6. However, a marked surge in both secretion and expression of IL-6 is noticeable during various neurological disorders, encompassing conditions like Parkinson's disease (PD) and Alzheimer's (AD) (Benveniste et al., 1998), instances of brain ischemia (Ali et al., 2000) and Multiple sclerosis (MS) (Frei et al., 1991). The absence of IL-6 signaling assumes a pivotal role in both inflammation and neuroprotection. This is exemplified by IL-6-deficiency in mice leading to the reduced glial activation following traumatic central nervous system (CNS) injury (Penkowa et al., 1997; Klein et al). However, it's important to note that IL-6 serves as a neurotrophic factor and fosters the differentiation of oligodendrocytes (Akaneya et al., 1995), contributing to the regeneration of peripheral nerves. These roles underscore IL-6's pro-survival influence within CNS disorders.

III. IL-6 AND RHEUMATOID ARTHRITIS

Rheumatoid arthritis (RA) is an autoimmune sickness impacting around 1% of the world-wide population. It manifests as inflammation and discomfort in the synovial joint tissues, and can potentially extend its effects to various other organ systems, such as the skeletal system, cardiovascular and pulmonary system. This condition often leads to notable

psychological repercussions. The underlying mechanisms of RA emerge from a complex interplay of mediators and inflammatory cells which serve as the targets for disease-modifying treatments employed to manage RA. The chief hallmark of RA is pain, which can be incapacitating. Enhancing pain relief has consistently ranked as the utmost priority for patients with RA in terms of health outcomes (Heiberg et al., 2005; 2002).

Numerous cytokines, such as tumor necrosis factor alpha (TNF α), interleukins (IL)-1, IL-6, and IL-10, are recognized for their affect on RA-related pain. Nonetheless, although pain in RA is predominantly attributed to inflammation driven by these cytokines in the joints, emerging evidence proposes that other factors, such as neuropeptides, and additional cytokines, might directly induce pain by affecting the nervous system. Notably, preclinical data underlines the significant role of IL-6, which could potentially contribute to pain associated with RA through diverse mechanisms, not solely through indirect means involving joint inflammation (Zhou et al., 2016).

Research findings indicate that rheumatologists frequently attribute pain in individuals with rheumatoid arthritis (RA) to either fibromyalgia or the underlying damage of the joint caused by RA. However, radiographic damage has been demonstrated to only account for 2.1% of reported pain in patients. Moreover, the proportion of RA patients meeting the criteria for fibromyalgia classification increases as the disease progresses, implying a role for central pain augmentation. While RA primarily involves joints, pain is often declared as extra-articular, possibly diffused, and even extending to nonarticular sites, thus varying in location and timing. This pain doesn't seem to be connected to synovitis and likely stems from central pain processing alterations (Flodin et al., 2016).

For astute clinicians, there are occasionally subtle indications that facets of pain in RA patients might stem from nervous system involvement. For instance, patients may describe pain sensations as tingling, burning, or sharp. The involvement of the central nervous system (CNS) is becoming more evident, as a substantial portion of RA patients exhibit some kind of recognizable involvement of neuropathic system. Additionally, autonomic neuropathy is linked with RA (Adian et al., 2014). These observations reinforce the idea that the CNS plays a significant role in RA. The evident disparities between inflammation and pain suggest that some RA-related pain might be an independent issue that overlaps with, but isn't exclusively due to, inflammation. The prevailing hypothesis is that pain in RA originates from some form of inflammation or injury. However, alongside this, RA patients experience pain that is independently triggered, transmitted through the peripheral nervous system, increased in the spinal cord, and felt in the CNS. Within the brain, external psychosocial factors intertwine with more distant sensations. This pain, distinct from inflammation-related pain, is partly attributed to cytokine dysregulation. The concept of RA—examining components apart from joint inflammation—is not new and extends beyond pain. Even when synovitis persists, radiographic progression is mitigated in patients taking IL-6 or TNF inhibitors. This suggests that these steps may be disconnected and addressable separately. Basically, although cytokines do trigger joint inflammation (which then causes pain), they also seem to produce different impacts on the peripheral and different components of the nervous system. These effects can lead to pain more immediately, even without a direct connection to inflammation. In this context, the cytokine IL-6 emerges as a critical player. In animal models of RA, increased levels of IL-6 have been noted in synovial fluid and serum. IL-6 has the capacity to activate primary afferent sensory neurons through trans-signaling, initiating the perception of pain. IL-6 signaling is tied to changes in nociceptive sensitivity, which might lower the

response thresholds of neurons, potentially leading to heightened sensitivity in the peripheral nervous system. Moreover, IL-6 contributes to the perception of pain in the central nervous system. This involves persistent signaling from sensitized peripheral neurons, causing an extended state of hyperexcitability in central nervous system neurons. Consequently, this phenomenon can result in conditions like tactile allodynia and hyperalgesia. These observations parallel findings in both experimental models of RA and individuals with RA (Woolf et al., 2011). The prevalent assumption has been that inflammation and joint damage primarily underlie the pain experienced in rheumatoid arthritis (RA). Consequently, the treatment approach has largely centered on addressing inflammation to simultaneously manage pain. However, recent research indicates that a multitude of mechanisms play a part to the genesis of pain in RA, with a significant role attributed to IL-6. Pain and inflammation disconnection within the context of RA exists, and the substantial burden of persistent chronic pain among RA patients suggests that alleviating pain should be accorded similar importance as preventing joint erosions. While rheumatologists are attuned to the presence of comorbid conditions such as osteoporosis and cardiovascular disease in RA patients, the notion of central nervous system (CNS) involvement as a comorbidity landscape is typically not considered. Yet, emerging evidence implies a paradigm shift towards recognizing nervous system involvement as a prevalent and consequential aspect that warrants independent consideration in patient care.

As our understanding evolves, it becomes evident that there is a requirement for further research aimed at investigating the enduring impact of central sensitization in RA and exploring potential strategies for its early prevention in the course of the disease.

IV. IL-6 AND ASSOCIATED VIRAL INFECTIONS

IL-6 is recognized as a pivotal cytokine during infections, standing alongside interleukin 1 (IL-1) as well as of tumor necrosis factor alpha (TNF- α). Concrete support for IL-6's significance in viral infections has emerged from experiments involving IL-6-deficient mice as models of infection. These studies have illustrated the indispensable character of IL-6 in ensuring the survival of mice infected with the influenza virus. IL-6 achieves this by supporting the maximum regulation of various aspects: the T-cell response, resolution of inflammation, lung repair by tissue transformation, the relocation and macrophages roles, prevention of cell death of the lung cells, and the monitoring of IgG isotype swapping.

Multiple accounts have emphasized IL-6's main function in virus infections. When, the *IL-6* was disrupted in mice infected with the vaccinia virus, it hampered the inflammatory reaction by diminishing the action of specific cytotoxic T-cells. Similarly, murine contamination due to VSV resulted in impairment of the production of definite IgG antibodies. Further evidence of IL-6's role in virus infections arose from studies involving lymphocyte choriomeningitis virus infection in mice, where either IL-6 or IL-6R activity was inhibited using precise monoclonal antibodies. In the later steps of contamination the helper cells both T and B types were adversely impacted, ultimately undermining viral clearance (Harker et al., 2011)

The IL-6 gene has been incorporated into the genomic structure of rabies virus through genetic engineering, offering an alternative experimental model to evaluate the significance of IL-6 during viral contaminations (Luo et al., 2018). In comparison to mice infected with the parental virus the normal mice infected with this engineered virus exhibited

heightened resistance against the viral infections. These animals displayed augmented permeability of the blood-brain barrier, an increased presence of specific cells (CD8-T and B-cells), elevated levels of antibodies, and an increased innate inflammatory response within brain, characterized by the upregulation of several genes stimulated by (*ISG15*, *OAS1*, *ISG20*, *MX2* and *OAS2*).

As a crucial indicator in the context of viral infections, an assorted collection of immune cell receptors involved in pathogen recognition are integral. These encompass toll-like receptors such as TLR:2, 3, 4, 7, 8, and 9, DNA receptors, nucleotide-binding oligomerization domain-like receptors and retinoic acid-inducible gene-1-like receptors. These receptors possess the ability to identify a variety of association of pathogens molecular patterns displayed by viruses which include sunmethylated CpG DNA, single and double-stranded RNA and envelope glycoproteins. Subsequently, this recognition triggers the transcription of IL-6 (Kawai and Akira, 2010; Tanaka et al., 2014).

Similarly, specific changes within a TLR-like structure in amino acids in the NS4B protein of a highly virulent classical swine fever virus (CSFV) strain brought about a significantly weakened effect in pigs. When pigs were infected with this altered CSFV strain, there was a consistent buildup of IL-6 in their tonsils. Through in vitro experiments involving externally added IL-6, it was confirmed that this cytokine can impede the replication of CSFV in the natural target cells for CSFV infection in pigs, which are swine peripheral blood mononuclear cells (Fernandez-Sainz et al., 2010).

Likewise, IL-6 antiviral affect was observed involving hepatitis B virus (HBV) during in vitro studies. These investigations demonstrated that externally introduced IL-6 possesses a direct ability to restrain the replication of HBV. This inhibition was evident through a noticeable decrease in the count of nucleocapsids containing viral genome. Moreover, by limiting the expression of the HBV receptor found in the human liver, IL-6 could impede HBV infection in hepatocyte, specifically the bile acid transporter Na(+)/taurocholate co-transporting polypeptide. Additionally, IL-6 effectively disrupted the epigenetic regulation of the nuclear cDNA mini-chromosome, leading to the inhibition of expression of hepatocyte nuclear transcription factors 1 and 4 alpha and also HBV transcription (Bouezzedine et al., 2015).

Nonetheless, scientific evidence also implies potential adverse effects that elevated IL-6 levels might impose on the cellular immune response against viruses. The clearance of viruses, ultimately promoting the establishment of a persistent viral state in infected hosts might be influence by the mechanisms associated with IL-6. Similar outcomes emerged with the introduction of an external source of IL-6, confirming the cytokine's potential to negatively modulate effector CD8 T-cell responses post T-cell activation. This inhibition was orchestrated through the STAT3 signaling pathway, which prompted the increase of suppressor of cytokine signaling (SOCS3). As a result, this diminished the STAT4 phosphorylation pathway induced by IL-12, which is crucial for the differentiation of effector CD8 T-cells (Wu et al., 2015).

V. CONCLUSION

Since the discovery of IL-6, extensive research has been conducted to explore its relationship with various diseases, which in time have yielded significant results. Evidence indicates that IL-6 levels increase to varying extents in specific illnesses, contributing to the onset and progression of inflammation, oxidative stress and vascular blockage. Though inflammation serves as a vital defense mechanism against infections, the accumulation of inflammatory cells at vascular lesion sites produces harmful substances that damage organs and potentially lead to conditions like cardiomyocyte and neuron swelling, or even death caused due to prolonged inflammation. Moreover, inflammation often coincides with oxidative stress, leading to excessive production of reactive oxygen species (ROS) that further harm cellular structures and contributes to disease development.

There is immense significance for preventing and treating numerous disorders in relation with the research on IL-6 and different diseases, as well as various pathological conditions. As studies progress and detection technologies improve, drugs or inhibitors targeting IL-6 are anticipated to offer promising therapeutic possibilities.

Notable advancements have been achieved in understanding the IL-6 receptor, yet several observations suggest that there's more to uncover about the receptor itself and how the IL-6 signal is transmitted in various cell types. Future research on IL-6 will need to elucidate how a single molecule can yield such diverse effects. It is hoped that this research will not only clarify IL-6's mechanisms but also provide new insights into signal transduction processes in general.

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