Interleukin-6 signalling as a valuable cornerstone for molecular medicine (Review)

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Abstract. The biological abilities of interleukin-6 (IL-6) have been under investigation for nearly 40 years. IL-6 works through an interaction with the complex peptide IL-6 receptor (IL-6R). IL-6 is built with four α-chain nanostructures, while two different chains, IL-6Rα (gp80) and gp130/IL6β (gp130), are included in IL-6R. The three-dimensional shapes of the six chains composing the IL-6/IL-6R complex are the basis for the nanomolecular roles of IL-6 signalling. Genes, pseudogenes and competitive endogenous RNAs of IL-6 have been identified. In the present review, the roles played by miRNA in the post-transcriptional regulation of IL-6 expression are evaluated. mRNAs are absorbed via the 'sponge' effect to dynamically balance mRNA levels and this has been assessed with regard to IL-6 transcription efficiency. According to current knowledge on molecular and nanomolecular structures involved in active IL-6 signalling, two different IL-6 models have been proposed. IL-6 mainly has functions in inflammatory processes, as well as in cognitive activities. Furthermore, the abnormal production of IL-6 has been found in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; also known as COVID-19). In the present review, both inflammatory and cognitive IL-6 models were analysed by evaluating the cytological and histological locations of IL-6 signalling. The goal of this review was to illustrate the roles of the classic and trans-signalling IL-6 pathways in endocrine glands such as the thyroid and in the central nervous system. Specifically, autoimmune thyroid diseases, disorders of cognitive processes and SARS-CoV-2 virus infection have been examined to determine the contribution of IL-6 to these disease states.

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1. Introduction

Interleukin-6 (IL-6) was first identified as a factor derived from T-helper type 2 (Th2) lymphocytes >40 years ago (1). On the basis of the biological abilities of IL-6 to stimulate B-cell differentiation, the interleukin was categorised among the B-cell stimulating factors (BSFs) and B-cell differentiation factors (BCDFs) (2). As a member of the BSFs, IL-6 was named BSF-2 and grouped together with BSF1 and interleukin-4 (2). IL-6 was included in the group of BCDFs due to its capacity to stimulate the secretion of IgM and IgG in B cells (3). After the nomenclature meeting held in New York at the end of 1988, BCDF/BSF-2 was finally referred to as IL-6 (4), as the biochemical properties of this factor showed an isoelectric point between 5 and 6 (2).

Over the last 40 years, several molecular features of IL-6 have been identified. Furthermore, new abilities of IL-6 have prompted its use as a target in medical practice for infective and cancerous diseases, including COVID-19. The present review highlights the current knowledge on the molecular and nanomolecular structures involved in active IL-6 signalling. By examining both inflammatory and cognitive IL-6 models, new properties of the IL-6 cytokine have been evaluated. Specifically, the cytological and histological locations of IL-6 signalling have been analysed together with serum

concentrations of IL-6 in order to distinguish between the classic and trans-signalling IL-6 pathways.

2. Three-dimensional shapes of chains involved in nanomolecular IL-6 signalling

Molecular analysis reveals that the human IL-6 gene is localized on the short arm of chromosome 7 (5). Depending on the genetic approach, IL-6 has been mapped to either the p21 or p15.3 region of the chromosome (6). By expanding from 22,725,889 to 22,732,002 base pairs, four introns and five exons were cloned in both human and mouse IL-6 genes (https://ghr.nlm.nih.gov/gene/IL6#location) (7). A polymorphic locus, Rs1800796, has been identified in the IL-6 promoter region (8). The recognition of genetic mutations in this genomic sequence has been used to assess human cancer risk (8).

In the 212-amino acid human IL-6 glycoprotein, 28 amino acids are linked to peptide signalling (https://www.genecards.org). The molecular mass of IL-6 is 23,718 Da, ranging between 21 and 30 kDa (https://www.genecards.org) (9-11).

The IL-6 topology is composed of a secondary structure that includes helicoidal motives related to four long α-chains. Via a bundle model, these α-chains are structured in three-dimensions to achieve the tertiary shape (9,12-14).

The bundle helicoidal complex is also observed also in a number of human cytokines such as IL-11, oncostatin M (OSM), ciliary neurotrophic (CNTF), leukemic inhibitory (LIF), cardiotrophin-like factor 1 (CT-1), erythropoietin, granulocyte colony-stimulating factor, IL-12, growth hormone, prolactin, IL-10, interferon and leptin (12). However, despite these factors adopting structures similar to the IL-6 bundle prototype model, they show little identity with the IL-6 amino acid sequence (12). By contrast, a viral homolog to the human IL-6 protein has been identified in herpesvirus 8 associated with Kaposi's sarcoma (15). This amino acid sequence is capable of arranging itself in a bundle helicoidal structure. This association is the reason that the viral protein is named viral IL-6 (15).

IL-6 works through interaction with the complex peptide IL-6 receptor (IL-6R). This receptor includes two transmembrane glycoproteins referred to as the IL-6Rα and gp130/IL6ß (gp130) subunits (16,17). Two different active genes contribute to the generation of human IL-6R.

Originally, the IL-6Rα gene was mapped on the long arm of chromosome 1 in the q21.3 cytoband (18) (Fig. 1). By counting 13 exons, this was cloned in 64,258 bases (https://www.genecards.org). The gene that codes for Gp130 is located on chromosome 5 at band q11 (19) (Fig. 1).

The IL-6Rα transcript encodes a modular glycoprotein made up of one α-chain with a size of 80 kDa, also known as IL6Q, gp80, CD126, IL6RA, IL6RQ, IL-6RA or IL-6R-1 (18). Specifically, IL-6Rα acts by binding the IL-6 ligand; however, this activity is not enough to transduce any signal (18). By contrast, the gp130 glycoprotein chain is unable to directly bind IL-6, but is capable of IL-6 signal transduction (19).

The assembly of IL-6 with its respective receptors occurs through a unique two-phase process. First, the four α-chains of IL-6 capture the α-chain of IL-6R with a dissociation constant (Kd) of ~1 Nm (20) (Fig. 2). In this stage, IL-6, composed of a dimeric structure, does not perform any signalling activity (21,22). The next assembly step is the construction of a hexameric cluster, where the complex of five α-chains binds gp130 with a Kd of ~10 pM (17,20) (Fig. 2). The previous binding of IL-6 with IL-6R occurs with lower affinity than that with the complex and gp130. In this second stage, the IL-6 complex is composed of a trimeric structure that, like in the first step, does not perform any signalling. To begin signalling, the IL-6/IL-6Rα/gp130 trimer proceeds through a homodimerization process that forms a hexameric complex (22).

These data suggest that the transition from low to high affinity IL-6 binding occurs due to phenomena pertaining to nanoparticle (NP) spheres. In fact, the geometric shape of the complex becomes crucial for the efficiency of binding at the nanometre scale (21,23). The five α-chains of the IL-6/IL-6Rα complex are only suitable for binding in a pentameric orientation. The hexamer is the competent form for energetic transition leading to the dimerization of the IL-6/IL-6Rα/gp130 cluster. Notably, the pentameric complex of α-chains, corresponding with the dimeric form of the IL-6/IL-6Rα structure, may appear either in the serum or in cellular compartments (Fig. 2). By contrast, the clusters of IL-6/IL-6Rα/gp130 are closed in cellular structures. The IL-6/IL-6Rα/gp130 complex is found in both the non-signalling trimer and signalling hexamer forms (Fig. 2) (23).

The trimeric model of IL-6 signalling is replicated in several other cytokines, including IL-11, LIF, OSM, CNTF and CT-1. This is due to their ability to bind gp130 on the cellular surface to elicit signal transduction (24). For these reasons, the physiological responses of these cytokines could occur simultaneously. These cytokines have been included in the group of L-6-type cytokine receptor mediators (24-26).

There are two main ideas that are inspired by the assessment of the nanomolecular structure of IL-6 signalling: Firstly, the nanomolecular shapes of the IL-6 system are largely independent of genetic composition. Therefore, genetic investigation has to be associated with nanomolecular evidence to completely track the physiological and pathological signals of IL-6. Secondly, the efficacy of IL-6 therapeutic targets is also dependent on the geometric shape of IL-6 signalling structures. Therefore, prior to determining the clinical benefits of IL-6 therapy, the nanomolecular conformations of IL-6 signalling have to be estimated.

3. Genes, pseudogenes and competitive endogenous RNA (ceRNA) for molecular control of IL-6 signalling

In contrast to the parental genes composing IL-6R, a distinct pseudogene was demonstrated for IL-6Rα and the gp130 gene (https://www.genecards.org) (19) (Fig. 2). These pseudogenes share much of their sequences with their corresponding parental genes (19). Conversely, pseudogene transcripts are equivalent to non-coding RNA or to antisense RNA and therefore are unable to produce biologically active proteins (27).

The IL-6Rα pseudogene, IL-6RP1, is found on the long arm of chromosome 9 at the locus q22.2 (Fig. 2). A repetition of gp130 sequence, IL-6STP1, is detected on the short arm of chromosome 17 and assigned at the p11 region (Fig. 2); this corresponds with a gp130 non-transcribed pseudogene (19).

IL6-STP1 transcripts have been shown to be involved in microbial defence processes (28). Via activation of the IL-6 family cytokines, IL6-STP1 stimulates inflammatory cells

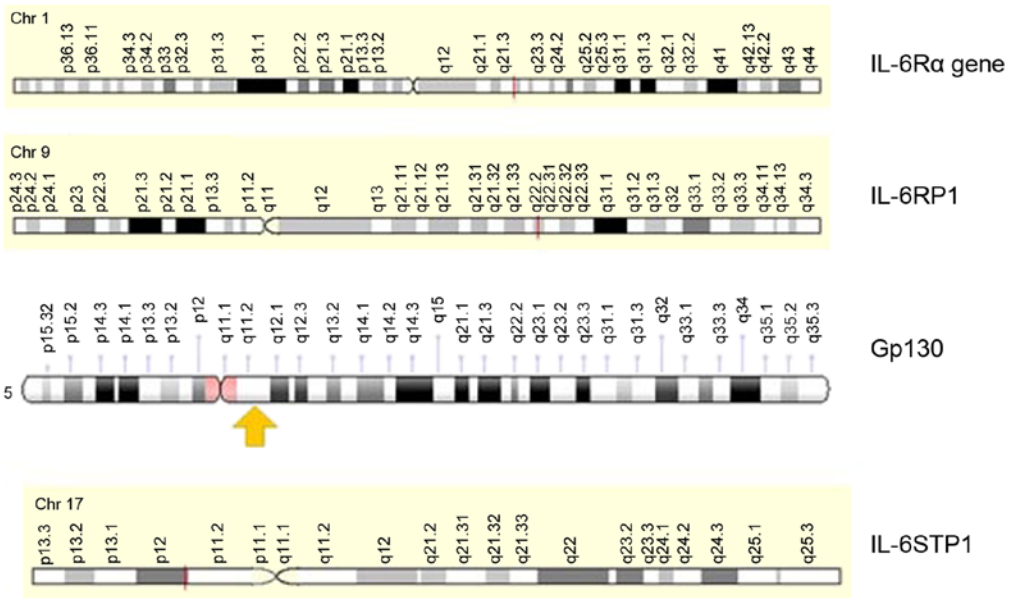

Figure 1. Chromosomal location of IL-6R genes and pseudogenes. Genetic diagrams for chromosomal location of IL-6Rα, IL-6RP1 and IL-6STP1 have been provided through the Genecards website (www.genecards.org) (104). To record Gp130 loci, Ensembl's GRCh38.p10 ideogram was used (105). IL-6Rα was found on chromosome 1 at loci q21.3 (red line). IL-6RP1 was detected on chromosome 9 q22.2 (red line). Gp130 was located on chromosome 5 at loci q11 (yellow arrow). IL-6STP1 was identified on chromosome 17 at loci p11 (red line). IL-6Rα, interleukin 6 receptor; IL-6RP1, interleukin 6 receptor pseudogene 1; Gp130, glycoprotein 130; IL-6STP1, interleukin 6 signal transducer pseudogene 1.

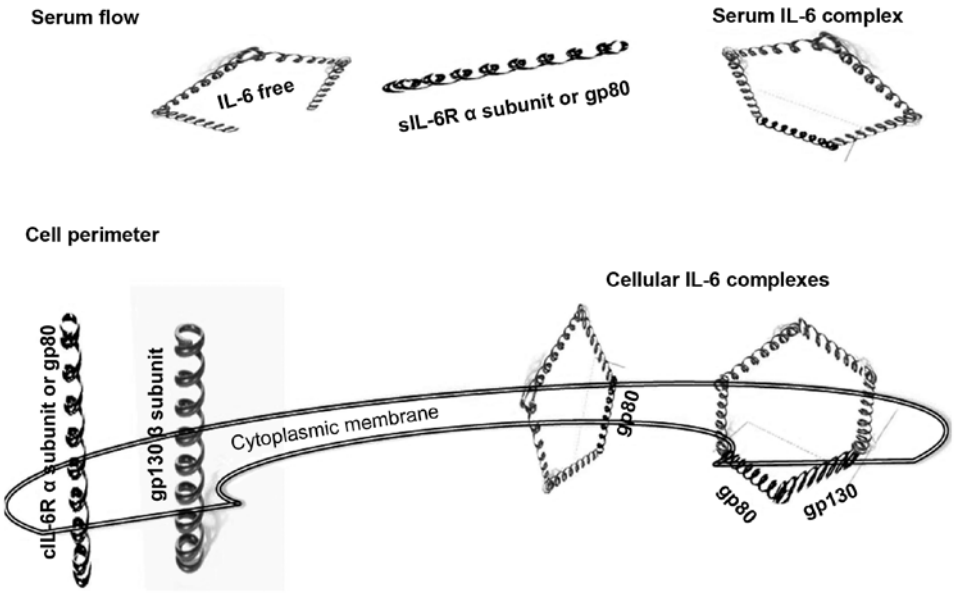

Figure 2. Location of IL-6 signalling components. A geometric representation of bonds that group the chains of IL-6 was designed. Pentameric and hexamer shapes were deducted in accordance with the number of chains pertaining to low and high affinity of IL-6 binding, respectively. Five chains composed the low-affinity IL-6 complex, whereas six chains composed the high-affinity IL-6 complex. IL-6, interleukin 6; IL-6 free, serum interleukin 6 unbound with IL-6 serum receptor; sIL-6R α subunit or gp80, serum receptor of IL-6 corresponding with an α-chain of 80-kDa; cIL-6Rα subunit or gp80, cellular receptor of IL-6 corresponding with an α-chain of 80-kDa; gp130 β subunit, 130-kDa glycoprotein.

to secrete acute-phase proteins (APP), including fibrinogen, a1-antitrypsin and hepcidin (28). In a mouse polymicrobial infection model, removal of IL-6STP1 caused inhibition of APP production associated with the dysregulation of the inflammatory response and an increase in mortality (28).

Pseudogene RNAs are part of an intricate network of competitive endogenous RNAs (ceRNAs) where all non-coding RNAs are assigned to two large groups: microRNAs (miRNAs) and long non-coding RNAs (27,29,30). miRNAs have <200 nucleotides, while long non-coding RNAs are >200 molecular bases. However, by using the same code, the full set of ceRNAs competes with parental mRNA (31).

ceRNAs absorb mRNA as a 'sponge' to dynamically balance mRNA levels for protein transcription efficiency (27,32). As a consequence, the ceRNA matrix serves to regulate protein expression (27,32). It is likely that ceRNAs mimic an ancient anti-viral defence biomechanism that appeared during the evolutionary scale of eukaryotic species

such as those in plants (33). For these reasons, ceRNAs are the cornerstone of recent molecular strategies that use 'silencing' genes to test cancerous biological aggressiveness, as well as to develop innovative molecular therapeutic approaches for cancer (27,34-37).

Data on the role of miRNA in the post-transcriptional regulation of IL-6 expression are gradually increasing (38). In line with the algorithms of miRanda, MicroCosm v5 and the TargetScan v7.1 database (http://multimir.org), 15 miRNAs profiles have been recorded to have potential involvement with IL-6 expression (38,39) (Table I).

In non-cancerous cellular models of polymorphonuclear leukocytes (PMNs) taken from cord blood and adult blood, post-transcriptional regulation of IL-6 expression was demonstrated by lethal 7g (let-7g) and miR-142-3p modulation (38). The let-7g gene has been located on chromosome 3 at loci p21 (40,41). This is a genomic region involved in carcinogenic processes of the lung (40,41). miR-142-3p has been associated with colorectal cancer and has been recorded on chromosome 17 at loci q22 (41). Let-7g and miR-142-3p have been found to be related with IL-6 expression, as both downregulate the production of IL-6 mRNA as well as protein (38). The role of miR-142-3p with regard to the endogenous expression of IL-6 has been previously predicted by mouse models (42).

In a cancerous cellular model and in normal controls, IL-6 overexpression was combined with decreases in let-7c, let-7d, let-7f, let-7g and mir-98 (43). Furthermore, all of these miRNAs were expressed in higher concentrations in the normal controls than in the cancerous cells (43). Finally, the let precursor let-7c exhibited a similar effect to let-7g in normal PMNs, as let-7c downregulated the mRNA and protein expression of IL-6 in the cancerous cells and controls (38,43).

In summary, the ceRNAs involved in IL-6 signalling play roles in the regulation of IL-6 expression in physiological processes and even in cancerous transformation of cells.

Table I. Data source for mioRNA profiles involved in the regulation of interleukin 6 expression.

miRNA	(Refs.)
hsa-let-7a	(38)
hsa-let-7d	(38)
hsa-let-7e	(38)
hsa-let-7f	(38)
hsa-let-7g	(38,39)
hsa-let-7i	(38)
hsa-miR-23a	(38)
hsa-miR-23b	(38)
hsa-miR-26a	(38)
hsa-miR-26b	(38)
hsa-miR-126	(38)
hsa-miR-132	(38)
hsa-miR-155	(38)
hsa-miR-142-3p	(38)
hsa-miR-146-a	(38)

hsa, *Homo sapiens*; let, lethal; miR/miRNA, microRNA.

4. Inflammatory and cognitive models of IL-6 cytokines

Since the identification of IL-6 in stromal, epithelial and muscle cells, new roles and functions have been attributed to this cytokine. It is clear that IL-6 could operate through paracrine, autocrine and endocrine mechanisms (44,45). As long as IL-6 signalling is detected in the endocrine and nervous systems, the model of function for the IL-6 inflammatory cytokine is changed; IL-6 may have roles in the regulation of endocrine secretion and in nervous impulse propagation (46,47).

IL-6 inflammatory model. IL-6 controls the inflammatory response primarily through orchestration of pro-inflammatory and anti-inflammatory effects (48,49). This is due to the activation of two different IL-6 pathways. The first is known as classic signalling, which operates in support of anti-inflammatory effects. Gp80 and gp130 are triggered through serum-derived free IL-6 in the cellular compartment (49). This pathway is dependent on cellular expression of the IL-6R components and the concentration of free IL-6 in the serum (Fig. 1) (49). The second trans-signalling pathway, promotes pro-inflammatory activities via IL-6 (49). In the serum compartment, free IL-6 recruits gp80 and the gp80/IL-6 complex activates cellular gp130 (Fig. 1) (49). Therefore, during trans-signalling with IL-6, a balance is maintained between the amount of serum gp80/IL-6 complex and the cellular expression of gp130 (49).

Expression of IL-6 associated with cognate receptor IL-6-Rα has been detected in cancerous and autoimmune endocrine diseases of the thyroid such as Grave's disease (GD) and Hashimoto's thyroiditis (HT) (50-53). In *ex vivo* pathological tissue, thyroid follicular cells exhibited intracellular IL-6 and IL-6-Rα. Greater immunoexpression of IL-6 and IL-6R were reported in cancerous follicular cells, as well as in HT and GD cases with high lymphoid infiltration (50-53). Simultaneous expression of receptor and ligand was not observed in normal follicular thyroid cells (50-53). To characterize classic and trans-signalling IL-6 in HT patients, free IL-6 and bound gp80/IL-6 complex levels were measured in the serum (48,49). Both IL-6 pathways appeared to be involved in the development and progression of HT. This was due to an increase in bound gp80/IL-6 in the serum of HT patients compared with that of healthy controls (48). Furthermore, free IL-6 was a candidate for an early diagnostic marker for the development of autoimmune disease in the HIV-seropositive (HIV^+) population (49). This was due to a high concentration of free IL-6 in the serum, which was correlated with the occurrence of autoimmune disease in HIV^+ subjects.

The inflammatory IL-6 model is frequently used to explain IL-6 modulation of the response to toxicity of nanomaterials (54). *In vitro* and *in vivo* studies have underlined the pro-inflammatory effects of several natural and synthetic NPs. Due to their capacity for internalization, inhalation of NPs actives several pathways that, in addition to causing apoptosis, fibrosis, genotoxicity and tumourigenesis, also causes strong inflammation at the lung level and beyond (55-59). Briefly, following phagocytosis by macrophages, the NPs trigger the response of other immune cells. The macrophages also release the inflammasome NLRP3, a multiprotein complex

whose activation is prompted by numerous different signals, including pathogen-associated molecular patterns and danger-associated molecular patterns (60,61). NLRP3 is activated by reactive oxygen species (ROS) overproduction and the inflammatory cascade continues since NLRP3, in turn, induces the expression of IL-6, IL-1β and TNF-α genes (62).

In the central nervous system, the NP induction of microglia activation causes the onset and progression of chronic brain inflammation, leading to a loss of neuronal cells and an increase in white matter abnormalities; this is associated with an increased risk for autism spectrum disorders, a lower IQ in children, neurodegenerative diseases, such as Parkinson's disease (PD), Alzheimer's disease and multiple sclerosis, and strokes (63). As demonstrated by Visalli *et al* (57) in the differentiated SH-SY5Y neuronal model, the exposure to synthetic NPs significantly increased transcript levels of IL-6, IL-1β and TNF-α, confirmed by the measurement of cytokine levels detected in the cell supernatants. The role of neuroinflammation and microglia activation in neurotoxicity was detected in an *in vivo* study using cortical stereotactic injection of carbon-based NPs into the mouse brain (64). According to Bussy *et al* (65) the brain region-specific sensitivity to NP exposure is most likely related to the number of microglial cells in the different brain regions.

IL-6 cognitive model. Two main sources have contributed to set the cognitive model of IL-6 cytokines: The cellular distribution and histological localization of IL-6/IL-6R signalling in brain tissue; and the different neurological responses to IL-6 serum concentrations due to activation of either the classic or trans-signalling pathway (66,67).

Normal neurons and microglia are able to secrete IL-6 polypeptide, as well as transcribe genomic IL-6-Rα mRNA (66). IL-6 has been implicated in the pathogenesis and cure of PD. Environmental exposure to pesticides also causes degeneration of dopaminergic neurons by activation of inflammatory cytokines such as IL-6 (68,69). The alteration of dopaminergic transmission produces a complex symptomology due to impairment of motor and cognitive performance. Several new medicinal plant extracts and phytochemicals, such as ellagic acid, are potentially suitable for use to alleviate PD symptoms due of their ability to decrease the anti-inflammatory activities of cytokines in cellular models (70,71)

Conversely, IL-6-Rα sequences have uniquely been detected in microglia and remain undetected in oligodendrocytes and astrocytes (66,72). In human and rat brain tissues, IL-6 was mainly localized in the hippocampal region (67,73,74). Several reports have associated the grey matter of the human brain with cognitive processes such as memory consolidation and learning, appearance of depression, post-traumatic stress and childhood maltreatment disorders (74-76). Under physiological conditions, the left hippocampus showed an association between decreased grey matter volume and an increase in serum IL-6 (74). An increase in right hippocampal volumes involving the head, parahippocampal gyrus and dorsal parts of the amygdala were associated with the IL-6 polymorphism rs1800795 (76).

In neurons and oligodendrocytes, the IL-6 response was mediated by trans-signalling (66). In microglia, the IL-6 classic and trans-signalling pathways were observed (67). In target brain cells neurons, IL-6 trans-signalling promoted neuronal degeneration (77,78). By contrast, the regeneration of neural tissue was mediated through IL-6 classic signalling via the involvement of microglia cells (66,78).

In summary, the classic and trans-signaling pathways are the basis of two models, the inflammatory and cognitive models, with cellular expression and serum levels of IL-6 used to distinguish between them.

5. Role of IL-6 in COVID-19

IL-6 is a cytokine with a number of different functions that plays a role in the host acute response to inflammation; it modulates host defence through numerous different mechanisms and actions directed towards monocytes, B cells and controlling homeostasis between Th1 and Th2 activity (75-79).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2; also known as COVID-19) primarily attacks airway and alveolar epithelial cells, vascular endothelial cells and macrophages in the lung, where there is expression of its host target receptor, angiotensin-converting enzyme 2 (80). Since IL-6 is relevant during infection that affects the mucosal sites, particularly at the upper and lower respiratory tract levels, it represents one of most important cytokines involved in the host response to SARS-CoV-2 infection (81). Severe COVID-19-induced pneumonia is marked by hyperactivation of the immune system and especially by excessive production of IL-6 (82,83). In this regard, several studies have revealed a strong correlation between high systemic levels of IL-6 and respiratory failure in severely affected patients with COVID-19 (84). According to these studies, a 2.9-fold higher mean IL-6 serum concentration was observed in patients with complicated COVID-19 compared with that in patients presenting with non-complicated disease. The strong correlation between IL-6 and COVID-19 has led to the consideration of serum IL-6 levels as potential diagnostic markers, disease severity stratification indicators and prognostic indexes (85,86). Moderately elevated IL-6 levels (>80 pg/ml) were, in fact, sufficient to identify COVID-19-infected patients and to predict progression towards respiratory failure. In addition, IL-6 has emerged as the most significant predictor of mortality in patients with COVID-19 (87).

The pathophysiological role of IL-6 in COVID-19 is well documented by several studies (83,88). IL-6 is generally considered the key driver of the hyperinflammatory process in COVID-19; it exerts effects on numerous different cellular targets that express a functional IL-6R, including T cells, B cells, vascular endothelial cells, monocytes and hepatocytes (79). By means of these actions on such a wide array of cellular targets, IL-6 mediates key effects on cellular immunity, exerting, at the same time, pro-inflammatory and anti-inflammatory functions (83,88).

The relevance of IL-6 is also demonstrated by the numerous studies that have explored its potential utility as a potential therapeutic target (89-93). The efficacy of a number of targeted monoclonal antibodies, directed against IL-6 or its receptor, is currently under investigation in several different countries. Numerous interventional clinical trials are, in fact, currently ongoing, using drugs that target IL-6, such as tocilizumab (Actemra) (38 interventional clinical trials, none of them yet with final and published

results; https://www.clinicaltrials.gov/ct2/results?cond=COVID-19+and+tocilizumab&age_v=&gndr=&type=Intr&rslt=&Search=Apply; accessed on 28 march 2021), sarilumab (Kevzara) (9 interventional clinical trials, none of them yet with final and published results; https://www.clinicaltrials.gov/ct2/results?recrs=&cond=COVID-19+and+Sarilumab&term=&cntry=&state=&city=&dist=; accessed on 28 March 2021), siltuximab (Sylvant) (1 interventional clinical trial; ClinicalTrials.gov identifier, NCT04329650) and clazakizumab (formerly ALD518 and BMS-945429) (6 interventional clinical trials, none of them yet with final and published results; https://www.clinicaltrials.gov/ct2/results?cond=COVID-19+and+Clazakizumab&age_v=&gndr=&type=Intr&rslt=&Search=Apply; accessed on 28 March 2021). These drugs act by inhibiting both classical and trans IL-6 pathways, and represent promising therapeutic options for the treatment of the most severe forms of COVID-19 (94-103).

6. Conclusion

In the present review, the molecular and nanomolecular structures involved in active IL-6 signalling were examined. Specially, the review reported that energetic transition from low to high affinity of IL-6 binding has to occur at the nanometre scale through changes of geometric orientation by conversion from the pentamer to hexamer shape.

The role played by miRNA in the post-transcriptional regulation of IL-6 expression has been evaluated through genes, pseudogenes and ceRNA of IL-6.

In addition, classic and trans-signaling pathways were analysed to evaluate the role of IL-6 in inflammatory and cognitive processes through anatomical localization and serum levels of active compounds in both pathways. Finally, the analysis of the pathogenic, diagnostic, prognostic and therapeutic roles of IL-6 in SARS-CoV-2 infection clearly demonstrates the central role of IL-6 in the ongoing global COVID-19 pandemic.

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Authors' contributions

MT, SS, AF, AV, GV and AP provided substantial contributions to the conception or design of the work, or the acquisition, analysis or interpretation of data. MT, SS, GV and AD were rewponsible for drafting the work or revising it critically for important intellectual content. All authors revised the manuscript and provided important intellectual contributions. All authors have read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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