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REVIEW

Cytokine receptors: structure and signal transduction

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SUMMARY

In the past 2–3 years, a number of cytokine receptors have been partly characterized and the cDNAs for the ligand binding chains cloned. This has revealed that cytokine receptors are complex. Many are known to be multichain receptors (e.g. IL-2) and since their mechanism of signal transduction is not obvious, it is likely that other proteins yet to be defined take part in the signalling process. The cloning of the receptor ligand binding chain has revealed that (unlike cytokines), there are major families of receptors. Some are members of the Ig supergene family (e.g. IL-1 receptor), others are members of the nerve growth factor receptor family (e.g. TNF), but the majority are members of the haematopoietic growth factor family (e.g. IL-3, GM-CSF). Yet other cytokine receptors do not belong to a family, e.g. IFN-γ.

Keywords cytokine lymphokine haematopoietic growth factor receptor signal transduction

INTRODUCTION

Cytokines are a group of usually short-range protein mediators which have important roles in the development, function and control of cells of the immune and many other systems. There is also now considerable evidence that they have a major role in the interactions between the immune system and other organs.

A common feature of all cytokines is their activity at low concentrations and the diverse range of activities that each of them can display. Cytokines transmit their biological signals to responsive cells by interaction with specific high affinity cell surface receptors. These receptors are expressed in very low numbers, usually a few hundred to a few thousand per cell, which have hindered their study. However, the last 5 years has seen very rapid progress in the biological characterization of these receptors due to the availability of recombinant cytokines, which have been radiolabelled to high specific activities, thus allowing extensive binding studies to be performed. One of the first cytokine receptors to be characterized was the IL-2R α-chain (p55 or 'TAC') using standard immunoaffinity protein purification technology, followed by protein sequencing, the generation of oligonucleotide probes and the screening of cDNA libraries. Similar techniques have been used for the cloning of human tumour necrosis factor (TNF) R and human interferon-γ (IFN-γ) R. Most of the cytokine receptors were cloned using expression cloning techniques where a mammalian cell line, transfected with a cDNA library, is screened either by antibodies to the receptor or by labelled cytokines. The cloning of either the human or murine receptor has usually led to the isolation of its counterpart.

The cloning of many receptors has indicated that there are three major receptor families: the haematopoietic growth factor receptor (HGFR) family, which includes the majority of cytokine receptors, the TNFR group, and members of the Ig-supergene family. Each family also contains receptors for molecules not usually considered to be cytokines. Thus the HGFR family includes prolactin and erythropoietin (EPO) receptors while the TNFR family includes nerve growth factor (NGF) R and the Ig superfamily includes a number of tyrosine kinase receptors. Some receptors, e.g. IL-2Rα chain and IFN-γ receptor, do not belong to any grouping. Within each family, most cytokine receptors show common functional and structural traits. The HGFR family are proteins responsible for the binding of a single cytokine, although many receptors require an additional protein to confer high affinity (e.g. IL-2R, IL-3R, IL-5R, GM-CSFR and IL-6R). The two most well-characterized receptors of the TNFR group show multiple binding chains and multiple ligands (TNFRs and NGFR, associated with tropomyosin receptor kinases). As for the IL-1R (Ig super family), this comprises two receptors, each recognising three ligands (IL-1α, IL-1β and IL-1 receptor antagonist).

There is still relatively little knowledge of the mechanisms by which cytokines transmit signals via their receptors. There is usually no obvious enzymatic mechanism within the receptor structure, and thus auxiliary molecules are thought to play a role, for example gp130 which is associated with the IL-6R, oncostatin MR and LIFR. However, gp130 also does not have any known intrinsic enzyme activity. There is no obvious common signal transduction mechanism within a given family. This leads to another basic question, which is how these cytokines express their great 'pleiotropicity'. In some cases, for example TNF, the existence of multiple receptors may explain this effect. However, for the majority of cytokines, the situation is still unclear.

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For the purposes of this review, we have dealt with the receptor groups by highlighting some individual members in each case. The review is confined to receptor structure and signalling.

THE HAEMATOPOIETIC GROWTH FACTOR RECEPTOR FAMILY

The haematopoietic growth factor receptor (HGFR) family comprises the majority of cytokine receptors: IL-2, IL-3, IL-4, IL-5, IL-7, GM-CSF and LIF receptors. The IL-6R and G-CSFR also have characteristics of the HGFR family and the Ig gene superfamily and thus will also be considered in this section. The HGFR family also includes proteins that do not bind ligand directly but modify receptor function, i.e. the gp130 (IL-6R β-chain) and the common β-chain of the IL-3, IL-5 and GM-CSF receptors.

The characteristics of this family are conserved cysteine residues in the extracellular domain, and a pentameric tryptophan-serine-X-tryptophan-serine motif—where X is any amino acid—just proximal to the transmembrane domain (Fig. 1). The receptors show some homology in their extracellular domains, but very little in the cytosolic domains. The latter lack known kinase or other enzymatic function. It is possible that other receptor-associated proteins perform this task (see below). Functionally, these receptors each only bind one ligand, and the majority display both high and low affinity receptors, although the basis for the dual affinities varies between receptors.

IL-2 receptor

IL-2, the major T cell growth factor, was one of the first characterized cytokines and its receptor has been the most studied (reviewed [1]). The receptors for IL-2 display many HGFR family characteristics, having both high ($K_d \sim 10^{-11}$ M) and low affinity ($K_d \sim 10^{-8}$ M), brought about by the heterodimeric structure of the receptor. The high affinity receptor comprises the IL-2R β-chain (p70) in conjunction with the previously characterized p55 α-chain (CD25), originally known as the TAC protein. The α-chain is not part of the HGFR family and has a short six amino acid cytoplasmic tail. On activated T cells, it is normally expressed at a 10-fold excess over the β-chain and on its own comprises the low affinity receptor. Proteolytic cleavage of the IL-2R α-chain gives rise to soluble receptors (sIL-2R) [2]. The β-chain binds IL-2, with an intermediate affinity of $K_d \sim 10^{-9}$ M. The high affinity of the heterodimer is obtained by combination of the fast association kinetics of the α-chain coupled with the low dissociation kinetics of the β-chain. Both the $\alpha\beta$ chain dimer and the β-chain alone are internalized on binding ligand and can mediate IL-2 activity. However the failure of the cloned β-chain to bind IL-2 when expressed in isolation in fibroblast, but not T cells has given rise to speculation of a third, 'γ-chain' of the IL-2R. Several reports have claimed to have identified such a protein as well as showing IL-2R association with class I HLA molecules, ICAM-1 and LFA-1 [1].

The key role of the IL-2/IL-2R in T and B cell proliferation has led to considerable study of its signalling mechanism. The IL-2R does not utilize the dual second messenger pathway of inositol triphosphate (IP_3)/Ca^{2+} and diacylglycerol/protein kinase C (PKC) [1], originating from the cleavage of phosphatidyl inositol bis-phosphate, as used by the T cell receptor. It has been reported that IL-2 can induce the generation of a myristilated diacylglycerol and inositol phosphate glycan from the hydrolysis of inositol glycolipid [3]. The involvement of tyrosine kinase activation has been reported by several groups [1] and IL-2 induces tyrosine phosphorylation of the IL-2R β-chain [1] and the serine phosphorylation of CD45 [4]. Moreover, the tyrosine kinase proto-oncogene $p56^{lck}$ has been found in association with the IL-2R β-chain [1]. IL-2 has also been shown to be able to activate $p21^{ras}$ [5] and also G-proteins [6], the c-raf serine/threonine kinase [7] and PI3 kinase [8]. In the nucleus, IL-2 has been shown to induce c-myb [9] and c-fos and c-myc [10]. However, the extent of the involvement of any of these observed intracellular biochemical changes to the IL-2R signal transduction pathway and their relationship to one another has yet to be established.

The IL-4 and IL-7 receptors

These cytokines are growth factors for activated T cells and mature (IL-4) and immature (IL-7) B cells [11]. The IL-4 receptor has been identified and cloned as a $\sim$140 kD molecule displaying a single high affinity binding ($K_d \sim 10^{-10}$ M) [12,13]. A low affinity receptor ($K_d \sim 3 \times 10^{-8}$ M) has been identified on human peripheral blood mononuclear cells [14], where cross-linking studies suggested that the low affinity binding was due to the presence of a putative 65/75 kD protein associated with the IL-4R. A low affinity IL-4 binding activity has also been isolated from culture supernatants [15]. However, these lower molecular weight IL-4R associated proteins may be, in part, proteolytic products of the main receptor protein [16]. The existence of high affinity sIL-4R has been identified in murine tissue fluids [17]. This is probably the product of an alternative splicing of IL-4R mRNA to produce a soluble truncated receptor [13]. However, the existence of such a sIL-4R mRNA has not been identified in human cells [12].

The IL-7R expresses a dual affinity with a high ($K_d \sim 5 \times 10^{-11}$ M) and a low ($K_d \sim 10^{-9}$ M) binding [18,19]. Park *et al.* [19] have suggested that the dual affinity is due to negative cooperativity of IL-7 binding and thus is observed when the cloned human or murine IL-7R is expressed in COS fibroblast cells [18]. A low affinity ($K_d > 10^{-8}$ M) IL-7R is also expressed on COS fibroblast cells but this appears to be the function of some other as yet uncharacterized receptor [18]. On human T cells, the IL-7R undergoes changes following T cell activation, being downregulated in number, and with a smaller 'second' form of receptor appearing. The expression of the novel receptor is found on all T cells that can respond to IL-7 as a growth factor [20]. Whether this second IL-7R is due to an alternative receptor or is the product of a different splicing of mRNA from a single gene is unclear. Alternatively spliced products of the cloned human IL-7R have been identified [18], producing a smaller membrane bound form and a putative sIL-7R.

IL-4 induced upregulation of CD23 in human tonsillar B cells appears to require Ca^{2+}, IP_3 and cAMP signals [21, 22]. These signals are not used by IL-4 to induce sIgM [22] which, with other evidence has led to speculation that the upregulation of CD23 and sIgM in human B cells is operated by different IL-4Rs and/or signal pathways. Unlike IL-2, IL-4 does not induce $p21^{ras}$ activity [5] and the utilization of tyrosine kinase by this

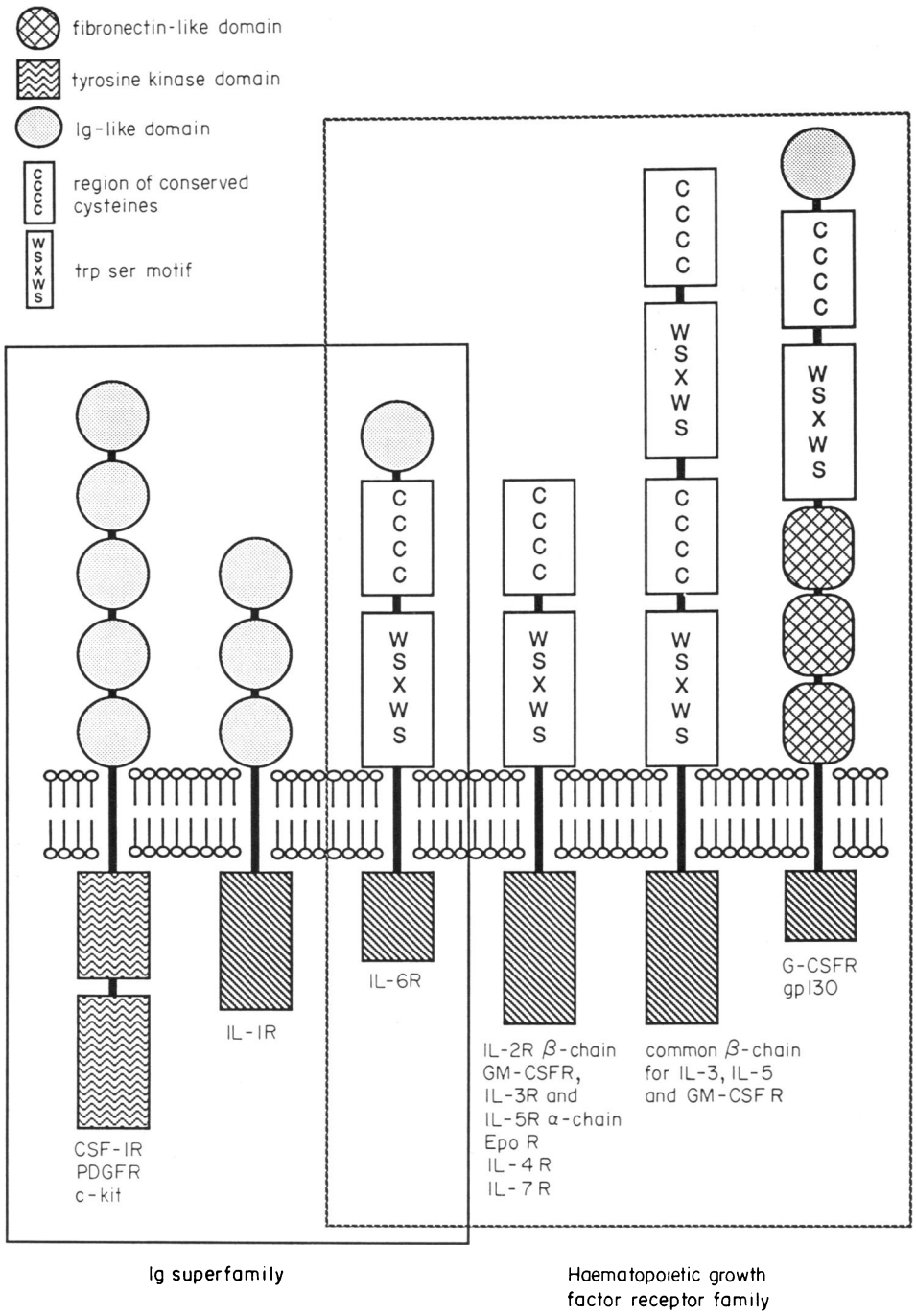

Fig. 1. Schematic representation of the members of the immunoglobulin superfamily and the haematopoietic growth factor receptor family. Members of the HGFRF are identified by the regions of conserved cysteines and the trp ser × trp ser motif where x is any amino acid in the extracellular domains.

receptor is unclear [23, 24]. However, the existence of multiple signalling mechanisms may account for these discrepancies.

The utilization of tyrosine kinases by IL-7R has been reported in mature T cells, lymphoblastic leukaemia T cells, thymocytes and B cells [25, 26]. The generation of IP_3 by IL-7 has been reported [25] in the latter three cell types, but this has not been confirmed in thymocytes and mature T cells [26]. No increases in intracellular Ca^{2+} associated with the function of IP_3 have been reported [26].

IL-3, IL-5 and GM-CSF receptors

IL-3 or GM-CSF are potent haematopoietic growth factors, IL-5 effects on B cell function are so far confined to the murine

system. These cytokines can all influence eosinophilopoeisis, with IL-5 the most potent. Binding and crosslinking studies had indicated that IL-3 and GM-CSF could partially cross-compete each other's binding and suggested the presence of common structural elements. All three receptors display dual affinity: high $K_d \sim 10^{-10}$ M and low K_d 10^{-8}–10^{-7} M. Their recent cloning has revealed the existence of heterodimeric receptor structures. In the human system, the smaller α-chains (~70 kD) of IL-3 [27], GM-CSF [28] and IL-5 [29] receptors, alone, express low affinity binding and are specific for each cytokine. The high affinity is the result of association of each α-chain with a common β-chain (140 kD) shared by all three receptors, which alone does not bind the cytokines [27,29]. As a refinement of this system, a second β-chain, 'AIC 2A', has been identified as a component of the murine IL-3R [30]; this protein shares 95% sequence homology with the common β-chain, AIC 2B [27,31,32], of the murine IL-3, IL-5 [33] and GM-CSF receptors. Unlike AIC2B, the AIC2A molecule binds IL-3 with low affinity [30].

Studies on the receptor signalling mechanism have shown that IL-3, IL-5 and GM-CSF induce tyrosine phosphorylation of a similar set of cytoplasmic proteins [23, 34]. Studies have also indicated that the β-chain of the IL-3R can be phosphorylated on tyrosine [35]. IL-3 and GM-CSF, like IL-2, are also capable of inducing the activation of $p21^{ras}$ [5].

The IL-6 receptor

The many functions of IL-6 include growth and differentiation activities on B cells, myeloma-plasmacytomas, T cells, hepatocytes and haematopoietic stem cells. The IL-6R shows dual affinity binding with high affinity receptors of $K_d \sim 10^{-11}$ M and low affinity receptors of $K_d \sim 10^{-9}$ M [36]. The cloning of an 80 kD receptor protein revealed structural elements of both the HGFR family and the Ig supergene family [36]. Further studies on the IL-6R structure revealed the existence of an auxiliary signalling molecule, gp130 (IL-6R β chain) [37]. This protein associates with the IL-6R/IL-6 complex and converts the receptor from low affinity to high affinity binding [38]. Cloning of the gp130 molecule has also identified this protein as a member of the HGFR family [38]. The involvement of the gp130 protein in IL-6R signalling was demonstrated using genetically engineered sIL-6R which, complexed with IL-6, associated with gp130 and induced IL-6 activity [37]. Since sIL-6R is also produced naturally [39], cells only expressing the gp130 but not IL-6R could possibly respond to sIL-6R/IL-6 complexes. Recently, gp130 was reported to act as an auxiliary protein for the oncostatin M and LIF receptors [40]. The gp130 does not encode any kinase or known signalling function although it does possess a GTP binding motif but this can be deleted without affecting function [41]. In fact, little is known of how the IL-6 transduces its signals. However, IL-6 does induce the tyrosine phosphorylation of gp130 [41].

G-CSF receptor

Cloning of the human receptor for this cytokine identified two integral membrane proteins of 759 and 812 amino acids produced from a single gene by alternatively spliced mRNAs; the two products differing in their cytoplasmic domains [42]. The mouse appears to produce only the larger receptor [43]. Like the IL-6R, the G-CSFR has structural relationship with the HGFR family and the Ig superfamily, and in addition, with fibronectin type III domains [42]. The cytoplasmic domains of murine G-CSF and IL-4 receptor show a reasonable degree of homology [43]. Both the cloned and native receptor show high ($K_d \sim 2$–5×10^{-10} M) and low ($K_d \sim 2 \times 10^{-9}$ M) affinity binding [44].

Other family members

As stated, the HGFRF includes receptors such as those for prolactin and EPO that are not classically considered to be cytokines and as such, will not be dealt with here in any detail. The importance of many of these cytokines would suggest a latent potential for the HGFR family to act as oncogenes. In this respect, Longmore *et al.* [45] have recently shown that a mutant EPOR which has a point mutation in codon 129, converting arginine to cysteine, can transmit a growth signal in the absence of ligand, and injection of a retrovirus encoding this receptor variant into mice produces erythrocytosis and splenomegaly.

TUMOUR NECROSIS FACTOR RECEPTOR FAMILY

This group of cytokine receptors comprises proteins with structural similarities to the two TNF receptors. The family is at present smaller than the HGFR family and some of these proteins are only presumed to be cytokine receptors. Besides the two TNFRs, the family includes the low affinity nerve growth factor receptor (L-NGFR) [46], the B cell antigen CD40 [47] and several proteins likely to be receptors, but which have no defined ligands; the T cell antigens OX40 [48] and CD27 [49], the Fas antigen, expressed on myeloid, T lymphoblastoid and fibroblast cells [50] and CD30, a marker for tumour cell lines derived from patients with Hodgkin's lymphoma [51]. Two other members, an open reading frame from Shope fibroma virus (SFV-T2) [52] and 4-1BB, a cDNA clone isolated from human T cells [53], have not been identified as proteins *in vivo*.

The structural definition of this family lies with an arrangement of three or four conserved cysteine rich sequences of approximately 40 amino acids (Fig. 2) in the extracellular domains. One or more of the repeats may be truncated, as in the p55 TNFR and the Fas antigen. In the main, there is no homology in the cytoplasmic domains of these proteins except for a region of 44 amino acids with sequence similarity present in the intracellular domains of Fas antigen, p55 TNFR and CD40 [50]. This region spans sequences that appear to be essential for receptor signalling in CD40 [54] and the p55 TNFR [55]. No identifiable regions for signalling functions, e.g. kinases, have been described. From the studies made on the two family members for which well-characterized ligands exist, TNFRs and NGFR, it appears that their receptors are complex, binding more than one ligand and exhibiting multiple receptors for a given ligand.

TNF receptors

Both TNF (TNF-α), and a second cytokine, lymphotoxin (LT/TNF-β) exhibit very similar activities, i.e. proinflammatory and

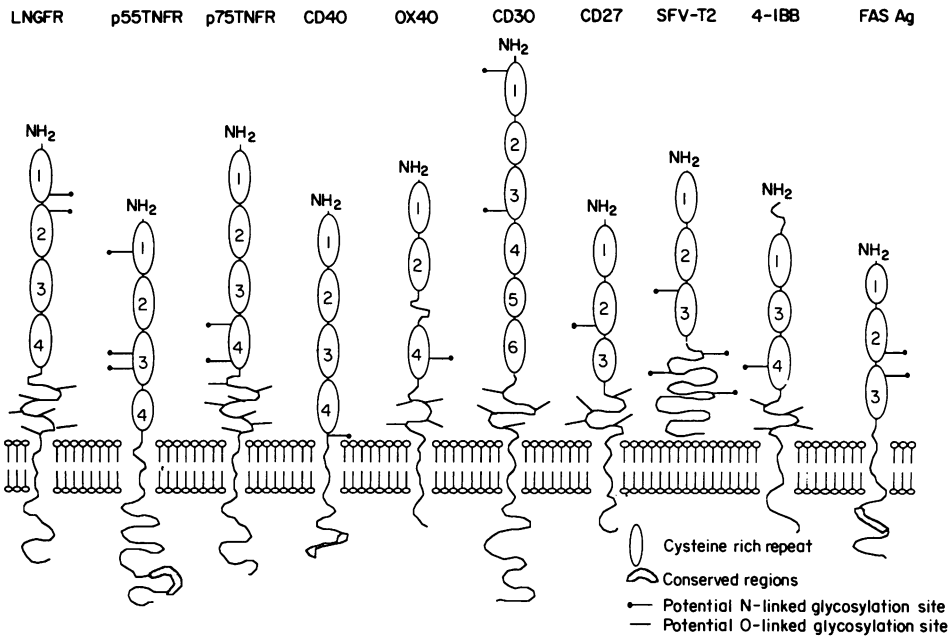

Fig. 2. Schematic representation of the members of the family of cell surface receptors related to the low affinity nerve growth factor receptor (LNGFR). TNFR, tumour necrosis factor receptor: SFV-T2, open reading frame from shope fibroma virus. The members are identified by the spatial arrangement of cysteine residues in the extracellular domains. Each of these repeated sequences consists of approximately 40 amino acids, some of which are also conserved between repeats and members. Repeat 4 of the p55TNFR, 1 of FAS antigen and 3 of 4–1BB are shorter than the other motifs and represented by small ovals. A region of homology has also been identified in the cytoplasmic domains of FAS antigen, p55TNFR and CD40, represented by stippled areas, which may be involved in binding accessory molecules.

cytotoxicity [56]. The main difference between the two cytokines is their source, TNF being mainly myeloid in origin whereas LT is mainly T cell derived. Receptor binding studies demonstrated that they cross-competed each other [57], and affinity crosslinking identified binding moieties of 55 and 75 kD expressed on the cell surface [58,59]. Binding studies on both receptors showed they had similar high affinity with K_d of 10^{-10}–10^{-11} M [59]. Cloning of the receptors led to the isolation of two proteins normally termed p55 (or p60) TNFR [60,61] and p75 (or p80) TNFR [62]. Both receptors are able to bind TNF and LT and cellular expression of the transfected receptor cDNA displays dual affinity binding. The observation that TNF has two distinct receptors has led to speculation that they may be responsible for the pleiotropy (multiple effects) of TNF and LT. Preliminary studies on murine cell lines where only one or other of the receptors is expressed [63,64], or transfection studies using the human p55 R [55,65] has suggested that this might be the case, with the p55 TNFR mediating cytotoxic function and the p75 receptor mediating growth promoting activity. However, studies on the expression of both receptors in various tissues have indicated that the two forms are normally co-expressed [59]. Both TNFRs also exist in soluble forms which have been identified *in vivo* [66]. The formation of sTNFR appears to be by proteolytic cleavage of the mature cell surface receptor [67] in a manner akin to the generation of sIL-2Rα-chain [2].

The nature of the TNFR signalling is quite different from what has so far been observed with the HGFR family. Firstly, both TNF and LT exist as trimers and would appear to bind receptors as such [68–70]. Secondly, unlike the HGFR family, anti-receptor antibodies can be agonistic as well as antagonistic. This has led to speculation that TNFR aggregation is a requirement for signalling, a hypothesis supported by the observation that agonist antibodies lose their stimulatory properties when used as Fab monomers [71]. The involvement of G proteins has been suggested from the induction of GTP binding activity and the inhibition by pertussis toxin of TNF effects [72]. This is followed by the elevation of cAMP [73] and indeed, pharmacological agents which increase intracellular cAMP concentrations have rendered cells more sensitive to TNF toxicity [74]. TNF also activates a serine kinase, causing the phosphorylation of serine residues of the p28 heat shock protein [75]. The involvement of tyrosine kinases in TNFR signalling however is unclear, with conflicting evidence being reported [76,77]. Several mechanisms by which TNF induces cytotoxicity have been proposed (reviewed in [78]) including reports that direct microinjection of TNF can elicit a response, suggesting that receptors are not always required for cytotoxic activity. However, this could not be reproduced in all TNF responsive cell types and is at odds with the existence of agonistic anti-receptor antibodies.

Other TNFR family members

Agonistic antibodies stimulate other TNFR family members, which suggests that receptor self association is required for signalling. CD40 appears to be linked to tyrosine kinase activity during B cell ontogeny [79]. The CD40 ligand has recently been defined as a T cell surface antigen, capable of inducing the

proliferation of splenic or tonsillar B cells and secretion of IgE by IL-4 stimulated B cells [80] while antibodies to CD40 also function with IL-4 in driving the release of soluble CD23 [81] and reversing the inhibitory effects of anti-CD19 antibodies, TGFβ and IFN-γ on IL-4 activity [82]. The full characterization of the other family members must await the identification of their active ligands. It is interesting to note that the recombinantly expressed SFV-T2 protein can bind TNF [83].

THE IMMUNOGLOBULIN SUPERGENE FAMILY

This group of receptors is characterized by Ig-like domains in the extracellular portion and includes many tyrosine kinase receptors: e.g. receptors for PDGF, EGF, insulin and insulin-like growth factors, the receptor for colony stimulating factor-1 (c-fms) and the Steel factor receptor, c-kit (Fig. 1). Several of these receptors have also been identified as proto-oncogenes, where mutated forms of the receptor have permanently activated tyrosine kinase activity. Some of these receptors, c-fms, PDGF, EGF and the insulin/insulin-like growth factors (IGF) are heterogeneous, with more than one form of receptor existing, for example, PDGFRα and β, which can combine in different forms, $\alpha\alpha$, $\alpha\beta$ or $\beta\beta$. In the case of the insulin receptor system, insulin, IGF-1 and IGF-2 can crossbind each others' receptors to a certain degree. The function and structure of these receptors will not be reviewed here. However, the second subclass of this family includes what is best described as the IL-1/IL-1R system, including three separate ligands and possibly up to three separate receptors. The IL-1Rs have no tyrosine kinase function in the cytoplasmic domain.

The IL-1 receptor system

IL-1 consists of two separate ligands, IL-1 α and β. They have a low amino acid identity (26%) but bind to the same cell surface receptors to induce a wide range of activities [84]. Recently, a third ligand IL-1 RA (IL-1 receptor antagonist) has been identified which acts as a receptor antagonist, binding with similar affinity to IL-1, but being unable on binding to transmit any signal [85]. Characterization of the IL-1R has identified two separate moieties [86]. The molecular cloning first identified an 80 kD form of the receptor which is expressed on T cells and fibroblasts and displays a single class of high affinity receptors ($K_d \sim 2 \times 10^{-10}$ M) [87]. However, a very high affinity form ($K_d \sim 5 \times 10^{-12}$ M) has also been reported on murine T cells and human keratinocytes [88]. A second smaller receptor (p60) has been identified on B cells and macrophages; this receptor appears to display dual affinity binding with high ($K_d \sim 5 \times 10^{-11}$ M) and low ($K_d \sim 10^{-9}$ M) affinity receptors [89]. Both forms of IL-1, α and β, bind both forms of the receptor with dual affinities. The third ligand, IL-1 RA, also binds IL-1 p80 and p60 with the same affinity as the agonistic ligands, but does not induce IL-1R internalization or IL-1 induced EGFR phosphorylation [90].

Signalling by IL-1 has been extensively studied, but there is no consensus on the mechanism(s) used by IL-1 to signal [91,92]. Studies have reported that IL-1 signalling is linked to the activation of a G protein, the elevation of cAMP, thus triggering protein kinase A (PKA) and culminating in activation of the NFκB transcription factor [91]. However, others have been unable to reproduce the utilization of cAMP and PKA by IL-1R although the activation of uncharacterized kinases has been reported with the induction of the serine phosphorylation of EGFR, IL-1R and hsp27 [92]. An interesting observation on the IL-1R is the ability to produce profound biological effects at very low ($\sim$1%) receptor occupancy [92].

Other cytokine receptors

While the majority of cytokine receptors fall into one of the three families described, there are two notable exceptions, the IL-2R α-chain and IFN-γR. The IL-2R α-chain was the first cytokine receptor to be identified and cloned and its role and involvement in IL-2R structure and function have already been discussed above. The receptor for IFN-γ also shows no homology to other receptors or any other known protein. IFN-γ has antiviral activity as well as effects on T cell differentiation, macrophage activity and upregulation of class II MHC expression and is also inhibitory to the function of IL-4. The IFN-γR has been characterized and cloned from murine and human cells as a 90 kD protein [93,94] and appears to bind IFN-γ as a dimer [95]. In common with other cytokine receptors it has no obvious means of transducing signals and thus it is assumed that other proteins are associated with the ligand binding chain to form the active receptor. Recent studies have indicated that a species specific accessory factor(s) is required for receptor signalling. In human, at least one of these factors appears to be encoded by Chromosome 21q [96] and in mouse by a gene on Chromosome 16 [97].

Signal transduction studies on the IFN-γR have implicated several second messenger systems including G proteins and adenylate cyclase, cAMP, calcium ion flux and protein kinase C, protein phosphorylation and Na^+/H^+ exchange [98] in the functioning of this receptor.

CONCLUDING COMMENTS

This review has highlighted the rapid progress in the important field of cytokine receptor research. However, it leaves many important questions open. For the majority of cytokines there is still no clear perception of how signals are transmitted across the membrane and of the chain of events into the nucleus. New families of cytokine receptors have been defined since this review was written, those for IL-8 and TGFβ. The field of soluble cytokine receptors, which represent the bulk of cytokine inhibitors, is becoming increasingly important, and cannot be described here.

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