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Phil. Trans. R. Soc. Lond. B 1990 **327**, 187-192
doi: 10.1098/rstb.1990.0053

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Phil. Trans. R. Soc. Lond. B **327**, 187–192 (1990)
Printed in Great Britain.

Structure, function, and regulation of the interleukin-2 receptor and identification of a novel immune activation gene

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This chapter is divided into two sections, the first dealing with a novel immune activation gene, denoted *Act*-2. This gene encodes a secreted protein that may represent a new cytokine. The Act-2 protein shares significant homology with proteins in two related families of small secreted proteins. Act-2 is rapidly synthesized by activated T cells, B cells and monocytes.

The second section deals with interleukin-2 receptors. These receptors are now known to be comprised of three distinct classes of receptors, formed by various combinations of two IL-2 binding proteins, the α and β chains. The low-affinity receptors contain α, but not β chains; the intermediate-affinity receptors contain β, but not α chains, and the high-affinity receptors contain both α and β chains. The β chain appears to be tyrosine phosphorylated. We discuss evidence for the existence of another protein of relative molecular mass 100000, which appears to be a subunit of at least the high-affinity receptor.

Act-2, a novel immune activation gene

An Act-2 ('Act' for activation) cDNA was identified within a cDNA library prepared from mRNA from activated human T lymphocytes (most of what follows is derived from Lipes *et al.* (1988)). The library was screened by using the method of differential hybridization to obtain cDNAs expressed in activated but not resting T cells. Act-2 cDNAs hybridize to a major mRNA species of approximately 0.9 kilobases (kb). Act-2 mRNA is strongly expressed in T lymphocytes activated with either phytohaemagglutinin (PHA) or anti-CD3 antibodies; however, its expression is not limited to T cells. Act-2 mRNA is also strongly induced in B lymphocytes stimulated with *Staphylococcus aureus* Cowan I, and in monocytes stimulated with lipopolysaccharide. Nevertheless, Act-2 mRNA is not expressed in all rapidly proliferating cells, as indicated, for example, by its lack of expression in various cell lines such as K562 cells. Analogous to the situation for interleukin (IL)-2 gene expression, Act-2 mRNA is not expressed in unstimulated Jurkat T cells or Jurkat T cells stimulated with either PHA or phorbol myristate acetate (PMA), but is expressed in these cells after stimulation with a combination of PHA and PMA. Furthermore Act-2 mRNA expression is not induced with serum in normal human fibroblasts, in contrast to c-*myc* expression.

Act-2 appears to represent one of the earliest immune activation genes. Act-2 mRNA can be detected within 15–30 min after stimulation of T cells with PHA, and levels peak after approximately 4 h. By sequential hybridization of a single Northern blot with probes corresponding to the c-*fos* and c-*myc* proto-oncogenes, the initial expression of Act-2 is detected as early as that of c-*fos*, whereas its peak expression approximately corresponds to the peak of c-*myc* expression.

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hu Act-2 (PAT744, huSIS$\gamma$) APMGSDPPTAC-CFSYTARKL-PRNFVVD-Y-YETSSL-CSQP-AVVF-QTKRSKQVCADPSESWVQEYVYDLELN
hu LD78 (huSIS$\beta$, PAT464)  ASLAADTPTAC-CFSYTSRQI-PQNFIAD-Y-FETSSQ-CSKP-GVIF-LTKRSRQVCADPSEEWVQKYVSDLELSA
muSIS$\gamma$                  APMGSDPPTSC-CFSYTSRQL-HRSFVMD-Y-YETSSL-CSKP-AVVF-LTKRGRQICANPSEPWVTEYMSDLELN
hu RANTES (huSIS$\delta$)      ASPYSSDTTPC-CFAYIARPL-PRAHIKE-Y-FYTSGK-CSNP-AVVF-VTRKNRQVCANPEKKWVREYI--NSLEMS
TY5 (muSIS$\alpha$)            APYGADTPTAC-CFSY-SRKI-PRQFIVD-Y-FETSSL-CSQP-GAIF-LTKRNRQICADSKETWVQEYITDLELNA
muMIP1$\alpha$                 APYGADTPTAC-CFSY-SRKI-PRQFIVD-Y-FETSSL-CSQP-GVIF-LTKRNRQICADSKETWVQEYITDLELNA
muMIP1$\beta$                  APMGSDPPTSC-CFSYTSRQL-HRSFVMD-Y-YETSSL-CSKP-AVVF-LTKRGRQICANPSEPWVTEYMSDLELN
muTCA3 (muSIS$\epsilon$)        KSMLTVSNSC-CLNTLKKEL-PLKFIQC-YRKMGSS--CPDP PAVVFRLNK-GRESCASTNKTWVQNH-L-KKVNPC
muJE                              APLTC-CYSFTSKMI-PMSRLES-YKRITSSR-CPKE-AVVF-VTKLKREVCADPKKEWVQTYI--KNLDRNQMRSE...
-----------------------------------------------------------------------------------------------------------------
huPF4                        EAEEDGDLQCLCVKTTSQ-VRP-RHITSLEVIKA-GPHCPTA-QLIATL-KNGRKICLDLQAPLYKK-II-KKLLES
boPF4                 ...LPADSEGGEDEDLQCVCLKTTSG-INP-RHISSLEVIGA-GTHCPSP-QLLATK-KTGRKICLDQQRPLYKK-IL-KKLLDGDES
raPF4                    VTRASPEESDGDLSCVCVKTSS-RIHL-KRITSLEVIKA-GPHCAVP-QLIATL-KNGSKICLDRQVPLYKK-II-KKLLES
huPBP                 ...GKEESLDSDLYAELRCMCIKTTSG-IHP-KNIQSLEVIGK-GTHCNQV-EVIATL-KDGRKICLDPDAPRIKK-IVQKKLAGDESAD
huIP-10                     VPLSRTVRCTCISISNQPVNP-RSLEKLEIIPA-SQFCPRV-EIIATMKKKGEKRCLNPESKAIKNL-L-KAVSKEMSKRSP
huGRO, MGSA                 ASVATELRCQCLQTLQG-IHP-KNIQSVNVKSP-GPHCAQT-EVIATL-KNGRKACLNPASPIVKK-IIEKMLNSDKSN
haGRO                       APVANELRCQCLQTMTG-VHL-KNIESLKVTPP-GPHCTQT-EVIATL-KNGQEACLNPEAPMVQK-IVQKMLKSGIRK
muKC                        APIANELRCQCLQTMAG-IHL-KNIQSLKVLPS-GPHCTQT-EVIATL-KNGREACLDPEAPLVQK-IVQKMLKGVPK
huMDNCF, NAF, 3-10C           SAKELRCQCIKTYSKPFHP-KFIKELRV-IESGPHCANT-EIIVKL-SDGRELCLDPKENWVQR-VVEKFLKRAENS
ch9E3, CEF-4        ALSQGRTLVKMGNELRCQCISTHSKFIHP-KSIQD-VKLTPSGPHCKNV-EIIATL-KDGREVCLDPTAPWVQ-LIV-KALMAKAQLNSDAPL
muMIP-2                     AVVASELRCQCLKTLPRVDF--KNIQSLSVTPP-G...
huNAP-1                  AVLPRSAKELRCQCIKT-SKPFHP-KFIKELRVIES-GPHCANT-EIIVKL-SDGRELCLDPKENWVQR-VVEKFLKRAENS
```

FIGURE 1. Act-2 is a member of one of two related families of small secreted proteins. The first two cysteines are either adjacent (top family) or are separated by a single amino acid (bottom family). Some sequences have more than one name. Abbreviations: hu, human; mu, murine; SIS, small inducible secreted protein; MIP, macrophage inflammatory protein; PF4, platelet factor 4; PBP, platelet basic protein; GRO, growth-related protein; MDNCF, macrophage-derived neutrophil chemotactic factor; NAP, neutrophil activating protein.

A full-length Act-2 cDNA was identified within a cDNA library prepared from mRNA from HUT-102B2 cells, a T-cell line transformed with human T-cell lymphotropic virus-I (HTLV-I). HTLV-I transformation appears to be a sufficient signal to induce Act-2 gene expression. The deduced amino acid sequence indicated an open reading frame of 92 amino acids. Radiolabelled sequencing of Act-2 protein expressed in a baculovirus expression system has shown that the first 23 amino acids of the open reading frame correspond to a cleavable signal peptide, and that the mature Act-2 protein is a secreted protein, 69 amino acids in length. Its calculated relative molecular mass (M_r) is 7808, although its apparent M_r on sodium dodecyl sulphate (SDS) polyacrylamide gels is somewhat greater. No potential *N*-linked glycosylation sites are present. The 3′ untranslated region of the cDNA has A–T rich consensus sequences that have been found in a number of cytokines and proto-oncogenes and which have been correlated with short mRNA half-life (Shaw & Kamen 1986; Caput *et al.* 1986), as appears to be the case for Act-2 mRNA.

When initially identified, comparison of the Act-2 sequence with other sequences in GenBank indicated that it was a unique gene product. Recently, two other groups have identified cDNAs derived from the same gene (Brown *et al.* 1989; Zipfel *et al.* 1989). The Act-2 protein shares homology with several other proteins that have been cloned. These sequences can be represented as members of two related families of small secreted proteins (figure 1). These families can most readily be distinguished by the absence or presence of a single amino acid interposed between the first two of four cysteine residues in the mature protein. Act-2 is part of a family that includes several factors secreted by T lymphocytes. The function for many of these products is still unknown or incompletely known and will require more investigation.

STRUCTURE, FUNCTION AND REGULATION OF THE INTERLEUKIN-2 RECEPTOR

The IL-2 receptor is now most correctly thought of as representing three distinct classes of receptors (see figure 2; reviewed in Leonard *et al.* (1989); Leonard & Sharon (1989)). Resting human T cells express predominantly intermediate-affinity receptors (K_D of 10^{-8} M), which

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contain the beta chain (IL-2Rβ, also known as p70), but not the alpha chain (IL-2Rα, p55, Tac antigen). In contrast, activated T cells express low-affinity IL-2 receptors (K_D of 10^{-8} M), which contain IL-2Rα, but not IL-2Rβ, and high-affinity receptors (K_D of 10^{-11} M), which contain both IL-2Rα and IL-2Rβ (see figure 2). These data regarding the subunit composition of the various IL-2 receptors are largely derived from affinity labelling studies in which ^{125}I-labelled IL-2 is bound and covalently cross-linked to cell-surface receptor proteins (Sharon *et al.* 1986; Tsudo *et al.* 1986; Teshigawara *et al.* 1987). Thus the indicated compositions should not be construed to imply anything regarding the stoichiometry of the different chains within each class of receptor. In addition, the above description does not deal with the possibility of other associated proteins, a topic that will be discussed below.

The high-affinity IL-2 receptors are generally believed to be the most important class of receptors in transducing the major proliferative signal(s) of IL-2. However, the intermediate-affinity receptors also are responsible for important biological responses on resting T cells and large granular lymphocytes (LGL). It has been known for several years that IL-2 is capable of boosting the natural killer (NK) activity of LGL, inducing the development of lymphokine-activated killer (LAK) activity of resting T cells and LGL, and inducing the proliferation of resting lymphocytes, all situations in which no high-affinity receptors were present. The discovery of the β chain has allowed at least partial elucidation of those dilemmas (Siegel *et al.* 1987). It has been possible to demonstrate that the cells in question were capable of binding IL-2 with intermediate affinity. Furthermore, cross-linking of ^{125}I-IL-2 to such cells resulted in the detection of only the β chain. Thus the induction of proliferative and cytolytic activities can be correlated with the binding of IL-2 to the β chain. It was further demonstrated that binding of IL-2 to the β chain resulted in the subsequent induction of the α chain and also an increase in the levels of the β chain (Siegel *et al.* 1987). Thus, although the α chain is believed to be inducible to a greater extent, it is clear that both chains can be induced in response to IL-2.

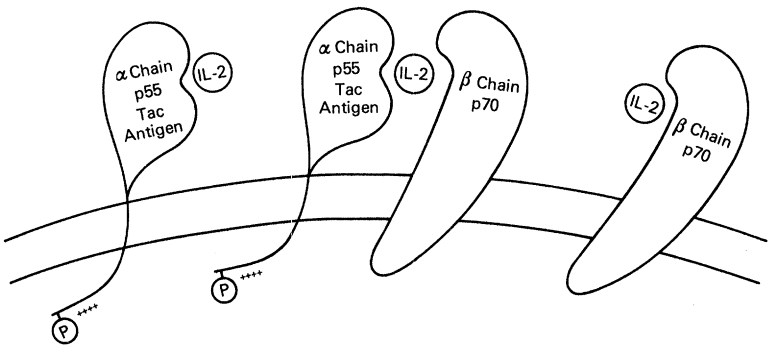

FIGURE 2. Minimal model for low, high and intermediate affinity forms of IL-2 receptors. Low-affinity receptors contain α, but not β chains, high-affinity receptors contain both α and β chains, and intermediate-affinity receptors contain β, but not α chains. As is indicated in the text, the stoichiometry of these chains within each type of receptor is unknown. Additional protein(s) are probably associated with at least the high-affinity receptor (see text).

Complementary DNAs encoding the α chain were identified in 1984 (Leonard *et al.* 1984; Nikaido *et al.* 1984). The deduced amino acid sequence for this protein indicated that its cytoplasmic domain is very short (only 13 residues), too short to encode a tyrosine kinase or other enzymic activity. In fact, this observation was one of the motivating factors that led our group to perform experiments resulting in the discovery of the β chain. Nevertheless, it is clear

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that IL-2 induces tyrosine phosphorylation events within the cell (Saltzman *et al.* 1988). The α chain is known to be a target for phosphorylation on serine 247 and threonine 250 (Shackelford & Trowbridge 1986), but no potential tyrosine phosphorylation sites are present (Leonard *et al.* 1984). Thus one important question was whether or not IL-2Rβ is phosphorylated and whether it represents a kinase. In order to investigate the first possibility, we initially digested an IL-2/IL-2Rβ complex with alkaline phosphatase. Such treatment resulted in a change in migration of the complex on SDS polyacrylamide gels, showing that IL-2Rβ is a phosphoprotein. Immunoprecipitation experiments and immunoblotting with anti-phosphotyrosine antibodies have strongly suggested that the β chain is constitutively tyrosine phosphorylated on YT and HUT-102B2 leukaemic cells (Sharon *et al.* 1989). However, we have no evidence in support of its representing a kinase, consistent with the deduced amino acid sequence for the β chain not containing a tyrosine kinase consensus domain (Hatakeyama *et al.* 1989). An important question is whether the phosphorylation of the β chain is regulated or constitutive, for example, whether phosphorylation or dephosphorylation occurs specifically in response to IL-2 or other stimuli.

Because of the high degree of responsiveness to IL-2 of the murine cell line CTLL-2, we decided to study this cell line in order to further investigate the inducibility of phosphorylation of the IL-2 receptor chains. In a previous study in which ^{125}I-IL-2 was cross-linked to CTLL-2 cells, a more complex pattern of cross-linking was seen than that expected for only α and β chains (Saragovi & Malek 1987). It was therefore a prerequisite to understand the basis for this pattern. When cross-linking experiments were performed, an intense band was identified that migrated at 115000 (Saragovi & Malek 1987; our unpublished observations). The ability to detect this species was obligately dependent on the binding of IL-2 to IL-2 receptors, as its detection could be blocked with an appropriate anti-IL-2 receptor antibody. As anticipated, this band was also detected in experiments using murine splenocytes activated with concanavalin A, but not in unstimulated splenocytes (where only the β chain was detected). Thus the detection of the band was correlated with high affinity but not intermediate affinity IL-2 receptors. To directly demonstrate that this band represents one 15.5 kilodalton (kDa) IL-2 molecule cross-linked to a novel 100 kDa species, we performed cross-linking experiments with biosynthetically labelled cells, unlabelled IL-2, and the thiol cleavable cross-linker, dithiobissuccinimidyl proprionate (DSP), and analysed samples on two dimensional non-reducing – reducing SDS polyacrylamide gels. In such a gel system, the cross-linker is cleaved in the second, reducing-condition dimension. We were able to directly identify a 100 kDa spot falling from the diagonal, indicating that the 115 kDa cross-linked band corresponded to IL-2 complexed with a new species that we denote p100. If cell surface proteins are cross-linked with DSP in the absence of IL-2, anti-α chain antibodies are capable of co-precipitating p100. Thus, not only can p100 be cross-linked to IL-2, but it can also be cross-linked directly to other IL-2 binding protein(s). These data also provide strong evidence in support of p100 representing an integral part of the IL-2 receptor (our unpublished observations). Although the available data on p100 remains limited, it is clear that it can be cell-surface iodinated and that it is a glycoprotein. Two important issues that await further investigation are whether p100 can directly bind IL-2 and the role(s) of p100 in IL-2 mediated signal transduction. We have not yet determined whether phosphorylation of the β chain is inducible and have not yet investigated whether p100 is a phosphoprotein or a kinase. Our data support the hypothesis that p100 may be preferentially associated with high affinity IL-2 receptors; more work is needed to definitively determine how it relates to low and intermediate IL-2 receptors.

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Other candidate associated proteins

So far, we have presented data in support of an α chain, a β chain and a murine p100 molecule. What other proteins may be associated with IL-2 receptors? Several candidates exist. First, we have demonstrated that HLA class I molecules can be cross-linked to IL-2, an event that first requires association of IL-2 with cell surface IL-2 receptors (Sharon *et al.* 1988). Although the physiological significance of this is unknown, it is perhaps relevant that anti-class I HLA antibodies have been reported to be capable of blocking IL-2 boosting of NK activity in certain cell lines. Second, using fluorescent energy transfer flow cytometric analysis, other investigators have suggested that the OKT27 antigen, now known to represent ICAM-1, is apparently associated with IL-2 receptors (Szollosi *et al.* 1987). It is certainly possible that other associated proteins may be identified. Whereas the role played by these various proteins is unclear, it is evident that the IL-2 receptor story is becoming an increasingly complex one. First, there are three classes of receptors with distinct biological roles. Second, the structures of these receptors are apparently complex. Third, despite this apparently large amount of information, the mechanism(s) by which IL-2 transduces its signals, and the identity of the tyrosine kinase that is known to be activated, all remain a mystery, rendering this growth factor–receptor system as one which is fascinating and in need of continued extensive investigation.

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