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Review

Interleukin-7 (IL-7) and IL-7 receptor (IL-7R) signalling complex in human solid tumours

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Summary. Interleukin-7 (IL-7) plays an important role in the normal development and maintenance of the human immune system. Its effects are mediated via its receptor, IL-7R. Ligand-receptor engagement results in a cascade of phosphorylation events mediated by various molecules including the Janus kinases (Jak1 and Jak3), PI3-kinase, Stats (signal transducers and activators of transcription) and other molecules. The activation of IL-7 signalling pathway results in survival, proliferation, differentiation and maturation of haematopoietic cells including B and T lymphocytes. Although the relationship of IL-7 with the development and differentiation of some haematological cancers like leukaemias and lymphomas is well recognised, little is known about it involvement with solid tumours. There are several studies that have revealed IL-7/IL-7R expression in epithelial systems and some human solid epithelial tumours. Furthermore, IL-7 can be produced by some human tumour cells and involved in tumour development and progression. In this review article we have summarised the main biological activities of IL-7 and its downstream signalling complex in relation to some human solid malignancies.

Key words: IL-7, IL-7R, Jaks, PI3K, Stats, Lymphangiogenesis, Breast cancer

Introduction

Interleukin-7, like other cytokines is a pleiotropic immune regulatory protein predominately produced by immune cells such as T-cells, natural killer cells, monocytes and stromal or non-haematopoietic cells. Generally cytokines are polypeptides of low molecular weight; their structures are often stabilized by N- and/or O-glycosylation and also by intra-molecular disulphide bridges. These molecules are important modulators and regulators of many immune cell functions. Cytokines act on many different target cells (pleiotropism) and frequently affect the action of other cytokines in synergistic or antagonistic ways. Their actions can be auto-, para- or endocrine depending on cell and tissue types via specific receptors on their target cells.

Interleukin-7 was first discovered at Immunex Research and Development corporation in 1988 (Namen et al., 1988a). Human cDNA was first cloned in 1989 (Namen et al., 1988b). In vivo studies revealed that IL-7 could accelerate lymphoid re-population and generation and lymphadenopathy in lymphopenic mice (Morrissey et al., 1991a,b), suggesting a role for IL-7 in lymphoid regeneration. These studies indicated that IL-7 has proliferative effects on the lymphoid populations and indeed it can lead to the development of lymphoprolipherative disease and peripheral and skin lymphomas, suggesting a potential role of IL-7 in tumourigenesis.

Malignant cells are surrounded by stroma and extracellular matrix which is composed of various cells like macrophages, lymphocytes, neurophils, fibroblasts, vascular endothelial cells as well as natural killer cells (Leek et al., 1994). All these cells including the malignant cells interact with each other via a complex network of extra-cellular signals, such as cytokines and growth factors and other protein molecules. These interactions are thought to regulate the proliferation and metastatic activity of malignant cells as well as modulate the host immune system towards the tumour cells (Hasday et al., 1990). Although the relationship between IL-7 and haematopoietic malignancies is well established, little is known about its interactions with solid tumours. Most data available to-date are in connection with the role of IL-7 as part of the immune system. It is still unclear whether IL-7 has other direct or indirect effects involved in solid tumours in terms of development and progression. This article will document the current knowledge of IL-7, IL-7R and their signalling complex in human solid tumours and their possible clinical relevance.

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IL-7 molecular structure and sites of production

Interleukin-7 is a single chain 25kD glycoprotein predicted to contain 4α helices that are internally disulfide cross-linked. Human IL-7 gene spans greater than 33Kb that is located at 8q12-q13 chromosome. The gene contains 6 exons and 5 introns and yields RNA transcripts of 1.8 and 2.4 kb. The gene encodes the IL-7 protein of molecular weight $2.5x10^3$ D. IL-7 molecule displays very high stability even with extreme pH variation (from 2.1 to 8.0) (Costello et al., 1993). However, it looses its biological activity after the addition of 2-mercaptoethanol, pointing to the importance of the disulfide bonds (Appasamy, 1999). Up to 4 isoforms have been described as products of alternative splicing, and predictions of their structure have been generated (Goodwin et al., 1989; Kroemer et al., 1998).

IL-7 is mainly produced by thymus (Namen et al., 1988a; Wiles et al., 1992). Other cells including bone marrow stromal cells (Funk et al., 1995), intestinal endothelium (Watanabe et al., 1995; Laky et al., 1998) and keratinocytes in the skin (Heufler et al., 1993) can also produce IL-7.

Biological activities of IL-7

IL-7 functions primarily as a growth and anti-apoptotic factor for B and T cells. It promotes the growth of B-cell progenitors (Namen et al., 1988b). It also stimulates B and T call lymphopoiesis (Appasamy, 1993; Costello et al., 1993). T cells require IL-7 for survival, as shown by the significant repression of T cell development in the IL-7-/- and IL-7R-/- knockout mice (von Freeden-Jeffry et al., 1995). It enhances the growth of natural killer (NK) cells and promotes growth and differentiation of T cells (Rich et al., 1993; Silva et al., 1994). It enhances the generation of cytotoxic T Cells (Alderson et al., 1990). It also stimulates the lytic activity of peripheral blood monocytes (Alderson et al., 1991). IL-7 can accelerate lymphoid regeneration in lymphopenic states as in AIDS patients (Carini et al., 1994) or after high dose chemotherapy or radiotherapy (Faltynek et al., 1992).

Cell maturation and differentiation induced by IL-7 are probably due to its trophic action by inhibiting apoptosis. It has been shown that T lymphocytes have failed to proliferate in response to alloantigen or phorbal myristate acetate and ionomycin in IL-7R-/- mice and instead these cells underwent apoptosis (Maraskovsky et al., 1996). Apoptosis, or programmed cell death, is a complex sequence of events mediated by either loss of an essential growth factor/cytokine or by the engagement of a death receptor with Fas and TNF. Apoptosis requires specific modulators like kinases and transcription factors as well as effectors like cysteine, proteases and caspases (Rowan and Fisher, 1997). When apoptosis was blocked, such as by the targeted deletion of p53 tumor suppressor gene in Rag-1-/- mice, early T cells survived much longer without a functional TCR (Jiang et al., 1996). Thus, it is more likely that a key function of IL-7 is to prevent thymic precursors from undergoing apoptosis. Cytokines which share the γc chain in their receptors, such as IL-2, IL-4, IL-9 and IL-15 are able to enhance survival under certain conditions rather than promote cell division (Boise et al., 1995). IL-7 may be maintaining the viability of cells by repressing a 'death-inducing' factor and/or activating a 'life-promoting' factor (Hofmeister et al., 1999). Furthermore, IL-7, and other γ_c cytokines, can rescue activated T cells from apoptosis by raising the levels of the anti-apoptotic proteins, Bcl-2 and Bcl-XL (Akbar et al., 1996). It is also possible that IL-7 could prevent cell death by inhibiting some pro-apoptotic proteins like Bid, Bad or Bax (Hofmeister et al., 1999). IL-7 can also act as a co-factor for V(D)J recombination in vitro in murine lymphoid precursors as murine stem cells derived from the bone marrow can perform full V-J joining of the TCR chain in the presence of recombinant IL-7 (Soloff et al., 1997). It has been shown that IL-7 and IL-7 receptor gene expression briefly precedes rearrangement of the immunoglobulin heavy and light loci, as well as TCR and loci in embryonic stem cell cultures (Potocnik et al., 1994).

IL-7 receptor (IL-7R)

IL-7 mediates its actions via engagement to its specific receptor, IL-7R, which is a heterodimer of an IL-7 binding chain, IL-7Rα and the γ_c chain, which is shared by the cytokine receptors for IL-2, IL-4, IL-9 and IL-15 (Goodwin et al., 1990; Noguchi et al., 1993; Kondo et al., 1994). Both IL-7Rα and γ_c are required for high affinity binding of IL-7 (Kondo et al., 1994). Human IL-7R gene is located on chromosome 5p13 (Venkitaraman and Cowling, 1992). The location of IL-7R gene is nearer to the location of growth hormone receptor, prolactin and a leukaemia inhibition gene that have similar signalling characteristics to IL-7Rα (Gearing et al., 1993). The molecular weight of IL-7R protein is 80 kD. Both IL-7Rα and γ_c have a pair of conserved extra-cellular cysteine residues and an extra-cellular Trp-Ser-X-Trp-Ser motif and lack intrinsic tyrosine kinase activity (Goodwin et al., 1990) and two partially conserved regions in the membrane-proximal part of their intracellular domains (Murakami et al., 1991). The γ_c chain is the functional component and it augments IL-7 binding to IL-7Rα chain (Noguchi et al., 1993). The IL-7Rα protein exists in two isoforms: membrane-bound and soluble forms. The membrane-bound isoform (P64) is also associated with IL-2Rγ_c (Goodwin et al., 1990; Noguchi et al., 1993). Binding assays have demonstrated the presence of two IL-7 receptor affinities: a high ($K_d \sim 10^{-10}$ M) and a low ($K_d \sim 10^{-10}$ M) affinity (Park et al., 1990).

The effects of selective blockage of IL-7 on cells expressing IL-7R has been attempted (Sweeney et al., 1998). Sweeney et al. have demonstrated that

DAB_{389}IL-7 is selectively cytotoxic for only cells bearing the IL-7R, which may serve a potential therapeutic agent against IL-7R bearing malignancies (Sweeney et al., 1998). The expression of IL-7R can also be further explored as a target for directed therapy such as IL-7R immunoconjugates in these malignancies. However, it has been demonstrated that IL-7 can induce signal transduction events in cells that do not express IL-7R because of its capacity to engage other surface receptors such as Flt3 and c-kit (Cosenza et al., 2002).

IL-7/IL-7R signalling pathway

The intracellular mechanisms mediating signalling of IL-7 are not yet clearly established. However, activation of IL-7R by IL-7 leads to series of intracellular phosphorylation events mediated by signalling molecules including the Janus kinases (Jak1 and Jak3), src kinases and Stats (signal transducers and activators of transcription) mainly Stats 5a/b (Dadi et al., 1994; Foxwell et al., 1995; Lin et al., 1995; Pernis et al., 1995) and to a lesser extent Stat3 (Pernis et al., 1995; Rosenthal et al., 1997) and Stat1 (van der Plas et al., 1996) (Fig. 1).

Src kinases are membrane-associated non-receptor protein tyrosine kinases. IL-7 activates the Src family kinases p59fyn and p53lyn in progenitor B and myeloid cells line (Venkitaraman and Cowling, 1992; Seckinger and Fougereau, 1994). $p56^{lck}$ is activated by IL-7 and the IL-7R is physically associated with both p59fyn and $p56^{lck}$ in human T cells (Page et al., 1995). IL-7Ra has no intrinsic tyrosine kinase activity that is necessary for the signalling pathway of IL-7 (Goodwin et al., 1990) although gc chain does have an src homology (SH2) domain that could play a role in the protein interactions during signalling (Taniguchi and Minami, 1993). However, it was found that this SH2 domain was not essential for triggering intracellular kinase activities by IL-7 (Lai et al., 1997).

Signal transduction starts with the specific binding of IL-7 to IL-7Rα, which heterodimerizes with the γc chain that is physically pre-associated with Jak3, which in turn phosphorylates both Jak1 and IL-7Rα. IL-7Rα also actively binds phosphatidylinositide-3'- kinase (PI3K). During activation, Stats are phosphorylated and rapidly dissociated from the receptor, form homo or hetero dimmers and rapidly translocate to the nucleus where they bind specific DNA and could regulate target gene transcription (Fig. 1). TSLP (Thymic Stromal Derived Lymphopoietin) is a molecule that could actively interact with the IL-7Rα chain and replace IL-7 in activating B-cell development independently from other molecules involved in IL-7 signalling (Ray et al., 1996).

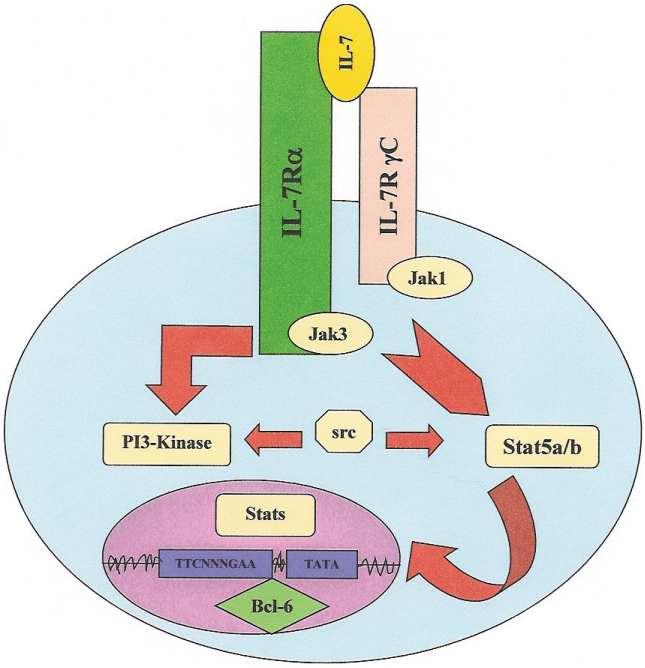

Fig. 1. Overview of IL-7 signal transduction. IL-7 is associated with IL-7Ra and γ_c and activate Janus kinases (Jaks). The Jaks in turn phosphorylate tyrosine-based docking sites on the receptor. Stats then bind via their src homology (SH2) domains. Stats are then phosphorylated by the Jaks, form homo-hetero-dimers and then translocate into the nucleus, where they bind target sequences like G-activated sequence (GAS) motif.

Janus kinases

The Janus family of kinases are a small group of proteins comprised of Jak1, Jak2, Jak3 and Tyke2. IL-7 signalling pathway mainly involves Jak1 and Jak3. As stated above, Jak1 is physically associated with IL-2Rα and Jak3 with the γ_c chain (Noguchi et al., 1993). The three-dimensional structure of the Jaks is still unknown. Structurally, Jaks are large kinases of more than 1100 amino acids with molecular weights of 120–130 kD. Their mRNA transcripts range from 4.4 to 5.4 kb. Multiple spliced forms of Jak3 have been identified, including a variant that lacks a segment of the catalytic domain (Gurniak and Berg, 1996). Jaks have seven regions of homology called Janus homology (JH) domains 1–7 and the carboxy-terminal tyrosine kinase, or JH1 domain, shares the features of other tyrosine kinase domains. For example, phosphorylation of tyrosine residues in the activation loop of kinases such as the insulin receptor play an important role in regulating phosphotransferase activity (Hubbard et al., 1994). While Jak1 has a wide range of tissue expression, Jak3 has a much more regulated and specific tissue expression (Ortmann et al., 2000). Jak3 is expressed at high levels in natural killer cells, thymocytes, T and B cells and myeloid cells (Gurniak and Berg, 1996). It has been demonstrated that Jak3 is expressed in breast cancer cell lines, primary breast cancer as well as colon and lung cancers (Cance and Liu, 1995). In addition to IL-7, Jak3 is also involved in IL-2, IL-4, IL-9 and IL-15 signalling (Zeng et al., 1994; Johnston et al., 1995).

There are three splice variants of Jak3 identified: B and M forms, which are expressed in epithelial cells and the S-form, which is mainly expressed in haematopoietic cells and has been implicated in IL-2R signal transduction (Lai et al., 1995). Jak3B was significantly autophosphorylated in a breast cell line, BT-474, in the absence of Jak3S, indicating that some other molecules could be involved in Jak phosphorylation in epithelial cells. Mice lacking Jak3 shows a dramatic immune deficiency similar to the gc , IL-7 and IL-7R knockout mice phenotype (Cao et al., 1995; Nosaka et al., 1995; Thomis et al., 1995; Baird et al., 1998). One study has revealed that lacking Jak1 does not alter activation of Jak3 and Stat5 (Higuchi et al., 1996), indicating that Jak-1 may not be essential in IL-7R signalling.

There are other types of proteins that were reported to interact with Jaks and mediate IL-7 signalling including Shc, Grb2, SHP-2, Vav, IRS, PI3-kinase, STAM, Pyk2 and others (Hofmeister et al., 1999). STAM (Signal Transducing Adaptor Molecule) is an adaptor molecule and was originally identified as a tyrosine phosphorylated protein that was induced by IL-7, IL-2, IL-4, IL-3 and GM-CSF (Takeshita et al., 1996). STAM contains an SH3 domain and an ITAM that is known to interact with the Zap-70 family tyrosine kinases. Jak3 is associated and could phosphorylate STAM (Takeshita et al., 1996, 1997). Pyk2, a member of focal adhesion kinase family, is physically also associated with Jak3. Therefore, Pyk2 is an important component in Jak3 signalling (Miyazaki et al., 1998). SLP-76 is another molecule that is thought to be important in IL-7 signalling as an adaptor molecule as mice lacking SLP-76 showed a profound block in thymic development and expansion of DP thymocytes, suggesting that SLP-76 is crucial for T cell development (Pivniouk et al., 1998).

PI3 -kinase

PI3K is a critical signalling molecule that regulates several cellular processes including survival and proliferation in different systems. PI3K is consisting of a regulatory p85 subunit and a catalytic subunit which phosphorylate the 3-ring position of PI-4,5-bisphosphate to generate PI-3,4,5-triphosphate (PIP3) (Toker and Cantley, 1997; Coffer et al., 1998). In addition to IL-7, other known activators of PI3K are PDGF, NGF, IGF-1 and PMA that act as survival factors suppressing apoptosis induced by a number of agents (Toker and Cantley, 1997; Coffer et al., 1998). Transfection of cells with constitutively active PI3K results in inhibition of apoptosis that is shown to be induced by c-Myc, UV radiation, TGF-ß and Fas (Kennedy et al., 1997; Eves et al., 1998; Hausler et al., 1998). PI3K activation of Akt/PKB and the subsequent phosphorylation of Bad could be the mechanism by which PI3k signalling could inhibit apoptosis. It has been shown that the accumulation of hepatocyte growth factor / Scatter factor (HGF/SF) in cancers, including breast cancer, observed in the most invasive and biologically aggressive cancers (Yamashita et al., 1994; Jin et al., 1997).This cancer cell cytoprotective function of HGF/SF is thought to be mediated by PI3K (Fan et al., 2000). Furthermore, PI3K has been proposed to mediate events such as mitogenesis, cell adhesion, motility and cellular differentiation as well as it provides protection against apoptosis (Toker and Cantley, 1997; Vanhaesebroeck et al., 1997). PI3K is also involved in the suppression of TNF induced apoptosis as demonstrated by kinase dead mutant PI3K construct that results in an enhancement of apoptosis (Burow et al., 2000). In breast cancer, there is a frequent activation of PI3K and ERa could bind its p85a subunit and activate the PI3K/AKT2 pathway in an oestrogen-independent manner (Sun et al., 2001).

Signal transducers and activators of transcription (Stats)

Stats are latent cytosolic transcription factors bind to the phosphorylated cytokine receptors via their SH2 domains (Greenlund et al., 1995). Stats family is composed of 7 members, Stat1, Stat2, Stat3, Stat4, Stat5a, Stat5b and Stat6 (Hoey and Grusby, 1999). Stats are approximately 750 amino acids long, but stat2 and Stat6 are lager (850 aa). As stated above, mainly Stats5 and to a lesser extent Stat3 and Stat1 are phosphorylated during IL-7R activation. They are stabilized by bivalent interactions with the Jaks and then homodimerize or heterodimerize and rapidly translocate to the nucleus to modulate specific target genes transcription.

Stat5 is encoded by two genes, Stat5a and Stat5b that share about 96% identity at the protein level (Liu et al., 1995). In addition to IL-7, prolactin, growth hormone, erythropoietin, thrombopoeitin, and IL-2 can also activate Stat5 (Ortmann et al., 2000). Stats5a/b co-localize on human chromosome 17 (Lin et al., 1996). The SH2 domain plays an important role in association between Stats and IL-7R. During IL-7 signalling, a conserved tyrosine (approximately 700 residues) from the N-terminus of stat5 is rapidly phosphorylated by the activated Jaks, allowing Stat proteins to form dimmers based on the interaction between the SH2 domain of each Stat and the phosphorylated tyrosine residue of the other stat.

The activity pattern of Stat5 in breast tissue suggests their active role in epithelial cell differentiation and milk protein gene expression (Liu et al., 1997). Stat5a knockout mice develop impaired mammary gland development (Liu et al., 1995, 1997). Furthermore, It has been shown that nuclear extracts from breast cancers display significantly higher levels of Stat5a in invasive breast cancers than those from benign and normal breast tissue (Watson and Miller, 1995), suggesting a possible enhanced IL-7 signalling in invasive breast cancer.

It has been revealed that inappropriate activation of specific Stats occurs with surprisingly high frequency in a wide variety of human cancers. Recent studies suggest that activated Stats signalling could be involved in oncogenesis by stimulating cell proliferation and

preventing apoptosis and aberrant Stats signalling may contribute to malignant transformation by promoting cell cycle progression and/or cell survival. Constitutive signalling by Stats has been increasingly associated with malignant progression (Bowman et al., 2000). Stats are also constitutively activated in cells stably transformed by a specific oncoprotein linked activation of the oncogenic Src tyrosine kinase to activation of Stat3 (Yu et al., 1995). This was confirmed by other studies that have demonstrated a correlation between activation of Stat3 and oncogenic transformation by Src (Cao et al., 1996; Chaturvedi et al., 1998). This finding has also raised the possibility that different oncoproteins of the tyrosine kinase family may also activate Stats during oncogenic transformation. Oncoproteins that may contribute to oncogenesis by activating specific Stats1 and Stat3 in fibroblasts are; v-Sis, v-Fps (Garcia et al., 1997), v-Ros, insulin-like growth factor I (IGF-I) receptor (Zong et al., 1998) and c-Eyk/v-Eyk (Zong et al., 1996; Wong et al., 1999). In epithelial cells, the cellular tyrosine kinase, Etk/BMX is able to activate Stat1, Stat3 and Stat5 (Wen et al., 1999).

Stat1 has a growth inhibitory function and therefore its activation in cancer may represent the remnants of a growth control pathway that has been overcome by the dominant growth promoting activity of another oncogene (Levy and Gilliland, 2000). This growth inhibitory role of Stat1 is consistent with the antiproliferative effects of interferon-γ that activates Stat1 (Bromberg et al., 1996; Buard et al., 1998; Grimley et al., 1998). Moreover, it has been demonstrated that mice with homozygous deletion of Stat1 are predisposed to some malignancies and develop tumours with more rapid frequency than their wild counterparts, suggesting that loss of Stat1 signalling further enhances oncogenesis (Kaplan et al., 1998). However, Stat1 could also induce oncogenesis via the possibility that its effects can be overcome by the simultaneous activation of the pro-proliferative effects of Stat3 or Stat5 that often accompany Stat1 in oncogenesis (Bowman et al., 2000).

Activation of specific Jaks and Stats has been demonstrated in several haematological malignancies including lymphomas and leukaemias (Migone et al., 1995; Gouilleux-Gruart et al., 1996; Weber-Nordt et al., 1996; Zhang et al., 1996). Constitutive activation of Stats have been demonstrated in human head and neck squamous cell carcinomas (Grandis et al., 1998), Myeloma cells and bone marrow extracts (Catlett-Falcone et al., 1999), prostate (Dhir et al., 2002), renal (Dhir et al., 2002; Horiguchi et al., 2002), lung (Fernandes et al., 1999), ovarian (Huang et al., 2000), pancreatic (Coppola, 2000) cancers as well as melanomas (Pansky et al., 2000) and in human breast carcinoma cell lines, but interestingly not in non-malignant mammary epithelial cell lines (Garcia et al., 1997; Sartor et al., 1997). Furthermore, it has been demonstrated that constitutive Stat3 activation in human breast cancer cells correlates with elevated EGF receptor and c-Src expression and activity (Garcia and Jove, 1998). Additionally, constitutive activation of Stats is also detected in metastatic lymph nodes suggesting a correlation with invasive tumours. Prolactin binding to its receptor leads to phosphorylation and activation of the Stat proteins, which in turn promote the expression of genes containing g-interferon activation sites (GAS) (TTCNNGAA). The activity pattern of Stats5a/b in breast tissue suggests their active role in epithelial cell differentiation and milk protein gene expression (Liu et al., 1997).

Negative regulators of IL-7 signalling pathway

IL-7 signalling can be interrupted by multiple proposed mechanisms like phosphatases Cytokine-inducible inhibitor molecules, transcriptional suppressors and Stat degredation (Fig. 2). These mechanisms are necessary to terminate an overactive cytokine signalling in order to prevent excessive maladapted response that might possibly lead autoimmunity or tumourigenecity.

SHP-1 has been proposed as a negative regulator that can downregulate cytokine signalling (Klingmuller et al., 1995; Haque et al., 1998). SHP-1 can either dephosphorylate Jaks or activated receptor subunits, depending upon the pathway activated (Ortmann et al., 2000). The inhibitor molecules, SOCS-1 (Suppressor Of

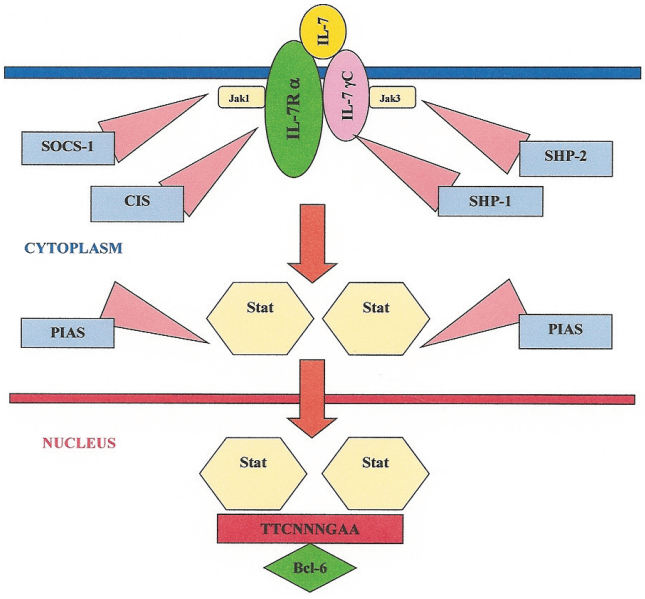

Fig. 2. Model of negative control of IL-7 signalling. Suppressor of cytokine signalling proteins (SOCS) can inhibit the Jaks. cytokine inducible src homology-2 protein (CIS) binds to activated IL-7R. SHP-1 can either inactivate IL-7R or the Jaks. Protein inhibitors of activated Stats (PIAS) are proposed to inactivate Stats. Stats themselves are also proposed to be degradated in the cytoplasm and/or nucleus by an unknown mechanism. Bcl-6 can bind to consensus Stat binding and represses the signalling pathway.

Cytokine Signalling) and CIS-1 (Cytokine Inducible src homology-2 protein) have been also identified as suppressors of cytokine signalling (Yoshimura et al., 1995). Subsequently, several other members of inhibitors have been identified (CIS2-CIS7/ SOCS2-SOCS7) (Hilton et al., 1998). These molecules are characterized by a central SH2 domain and a carboxy terminal region of homology called the SOCS box. Some SOCS members bind the phosphorylated activation loop tyrosine residue in Jaks, thereby inhibiting Jak activity (Takeshita et al., 1997). CIS-1 may downregulate cytokine signalling by binding directly to receptors, rather than Jaks. Recently, CIS-1 transgenic mice have been created, and their phenotype is remarkably similar to those of Stat5a/b knockout mice, indicating the role of CIS-1 as a negative regulator of Stat5 function (Matsumoto et al., 1999). Furthermore, SOCS members may play a role in non-cytokine signalling, including the leptin, growth hormone, and prolactin signalling pathways (Pezet et al., 1999). Additionally, CIS/CIS1 negatively regulates Stat5 activation (Matsumoto et al., 1997). Interestingly, CIS/CIS1 transgenic mice exhibit defects in signalling in response to IL-2 and prolactin quite similar to defects found in Stat5 deficient mice (Matsumoto et al., 1999). The promoter region of CIS/CIS1 has Stat5 responsive elements, leading to Stat5 dependent expression of this gene (Matsumoto et al., 1997). Some SOCS proteins bind directly to Jaks, whereas CIS can bind to activated receptors and prevent docking by Stats (Ortmann et al., 2000). Another family of inhibitors called Protein inhibitors of activated Stats (PIAS), PIAS1 and PIAS3, which inhibit Stats' function by an as yet unknown mechanism (Chung et al., 1997).

Inhibition of the downstream signalling of Jaks has been shown to abrogate constitutive Stat3 DNA binding, inhibit cell proliferation and induce apoptosis in human breast carcinoma cell lines (Garcia et al., 2001), moreover expression of dominant negative Stat3 in these cells induce growth arrest and apoptosis (Garcia et al., 2001). These data suggest a critical role for Stats in oncogenic signalling by the Jaks during progression of breast carcinoma. It has been shown that lack of stat5a could lead to the deregulation of one or several genes critical for normal breast development (Liu et al., 1997). Degradation of Stats is one way by which the Jak-Stat pathway can be negatively regulated. There are several proposed mechanisms to do so; dephosphorylation by phosphatases, cytokine-inducible inhibitor molecules, transcriptional repressors, and Stat degradation (Heinrich et al., 1998; Ortmann et al., 2000).

The accumulation of Stats in the nucleus can also be regulated at the level of nuclear import, export, or a combination of the two, the mechanisms that control these processes are not well characterized (Ortmann et al., 2000). Bcl-6, frequently associated with non-Hodgkin's lymphoma, has also been recently shown to downregulate Stat function and Bcl-6 deficient mice develop a severe systemic inflammatory disease, which is characterized by infiltrates of immunoglobulin E-bearing B cells and eosinophils (Ye et al., 1997).

The development of assays to detect activated Stats in these tumours may be of benefit in terms of diagnosis, treatment as well as assessing prognosis. Assays developed to detect activated Stats might include DNA binding assays and the development of antibodies designed to detect the activated phosphotyrosine could be used to compare normal and tumour tissues by immunohistochemistry (Bowman et al., 2000). Furthermore disruption of Stats signalling might constitute an attractive target for prevention and treatment of human solid cancers. Tumours with constitutive activation of Stat3 and Stat5 are predicted to be resistant to chemotherapeutic modalities, therefore, the development of selective inhibitors of Stats activation to be used in combination with more conventional chemotherapy may be a promising anti-cancer therapeutic modality (Bowman et al., 2000).

IL-7 and malignancies

Haematopoietic malignancies

IL-7 is known to potentiate the progression of some types of lymphomas and leukaemias. Studies on such malignancies indicate that IL-7 could stimulate the growth of both B and T acute lymphoblastic leukaemia (ALL) cells in vitro (Touw et al., 1990; Eder et al., 1992) and chronic lymphoblastic leukaemia (CLL) (Frishman et al., 1993b). It has also been shown that IL-7 increases DNA synthesis in acute (AML) and chronic (CML) myeloid leukaemia cells (Digel et al., 1991). Other studies have demonstrated that IL-7 is also able to stimulate proliferation of cutaneous T cell lymphoma (Sezary syndrome) (Dalloul et al., 1992; Qin et al., 2001) as well as Hodgkin's disease (Foss et al., 1995). Other neoplastic associations with IL-7 include its production by chronic lymphoblastic leukaemia cells (Frishman et al., 1993a) and Burkitt's lymphoma cells (Benjamin et al., 1994) and it has been shown to be elevated in the serum of Hodgkin's patients (Trumper et al., 1994). IL-7 transgenic mice develop a progressive cutaneous lymphoproliferative disorder as well as generalised lymphoproliferation that progress to malignancy making IL-7 as an oncogene in the living organism (Rich et al., 1993). Furthermore, a recent study has suggested a pathogenic role for IL-7 and IL-7R in the development of thyroid lymphoma (Takakuwa et al., 2000).

IL-7 and human solid tumours

Expression of IL-7 in tumours

IL-7 mRNA is expressed in colorectal (Watanabe et al., 1995; Maeurer et al., 1997), oesophageal (Oka et al., 1995), renal (Trinder et al., 1999), head and neck squamous cell carcinoma (Paleri et al., 2001) as well as Warthin's tumour of parotid gland (Takeuchi et al.,

1998). However, IL-7 mRNA was not expressed in breast cancer cell lines, tissues or normal breast tissues (Green et al., 1997). IL-7R mRNA is expressed in breast, lung, colon, renal and CNS cancer cell lines (Cosenza et al., 2002). Recently, it has been revealed that IL-7 can stimulate the proliferation of prostatic cells in benign prostatic hyperplasia, a benign prostatic enlargement, by increasing growth patterns of the fibromuscular tissues in the prostate similar to that of wound healing (Kramer et al., 2001). In melanomas, IL-7 mRNA was detected in more than 60% of tumours (Mattei et al., 1994).Transfection of the IL-7 gene in human melanoma cell lines was successfully performed using a retroviral vector showed an unaltered expression of MAGE-1 and MAGE-3 antigens and a retarded growth in T cell deficient mice (Miller et al., 1993).

Production of IL-7 in tumour cells

As stated above, IL-7 is produced *in vivo* by normal human intestinal epithelial mucosa and stimulates the proliferation of lamina propria and intra-epithelial lymphocytes (Watanabe et al., 1995). IL-7 is also produced by colorectal cancer tissues and promote the expansion of tumour infiltrating lymphocytes (TIL) in these cancers (Maeurer et al., 1997). The activity of the tumour infiltrating lymphocytes (TIL) is thought to be regulated by cytokines. TIL is composed of helper T $CD4^+$ cells, B lymphocytes as well as natural killer cells. Some reports indicated that IL-7 increases TIL in colorectal cancers, which might carry some prognostic implications (Maeurer et al., 1997).

Expression of IL-7R in tumour cells

It has also been shown that Intestinal epithelial lymphocytes are completely absent from IL-7Ra knockout mice, but only partially absent from IL-7 knockout mice (Fujihashi et al., 1997), suggesting a possible more significant role for IL-7R in intestinal lymphocyte proliferation. As stated above IL-7R is expressed in breast, lung, colon, renal and CNS cancer cell lines (Cosenza et al., 2002). Recently, we have shown that the expression of IL-7R is elevated in breast cancer tissues and that the levels of expression is associated with tumour size and nodal involvement in breast cancer (Al-Rawi et al., 2002a). Furthermore, we have demonstrated that IL-7 is a putative lymphangiogenic factor to human endothelial cells (Al-Rawi et al., 2002b), suggesting a possible direct effect of IL-7 on the endothelial cells within tumours and hence IL-7 might play a pivotal role in tumour angiogenesis and/or lymphangiogenesis.

Therapeutic value

It has been shown that intravenous IL-7 administration (5 μg twice daily for 20 days) to mice with metastatic breast cancer had no therapeutic effect, however it has prolonged survival if chemotherapy was given to these mice, but this was due to more rapid lymphoid reconstitution with IL-7 treatment (Talmadge et al., 1993). In another study, mammary adenocarcinoma tumour cells co-transfected with IL-7 and B7.1 resulted in a high level of protective immunity compared with IL-7 or B7.1 transfection alone or corynebacterium parvum (Cayeux et al., 1995).

Furthermore, IL-7 transduced tumour cells administered intra-tumourly in conjunction with dendritic cells creates potent anti-tumour responses to lung cancer in a murine model (Sharma et al., 1997). IL-7 gene transfer in non-small cell lung cancer in vitro significantly augments T lymphocyte activities, inhibits tumor cell proliferation and modifies tumor cell surface phenotype, suggesting that IL-7 gene therapy may be effective in modifying host anti-tumor responses in non-small cell lung cancer (Sharma et al., 1996). IL-7 could also enhance TIL in renal cancer (Sica et al., 1993). In addition, IL-7 could potentiate the growth and production of interferon g from human renal cell carcinoma reactive TIL and to a lesser extent enhance IL-2 induced lymphokine activated killer activity of TIL in renal carcinoma (Sica et al., 1993). Further in vivo studies in mice have revealed that administration of recombinant IL-7 (10mg twice daily for 7 days intraperitonially) resulted in a 75% reduction in pulmonary metastases from renal carcinoma (Komschlies et al., 1994).

One *in vivo* study, administration of IL-7 (5ng twice daily) in mice with melanoma has been shown to decrease primary tumour size and metastatic lesions, but did not affect survival unless administered in combination with hyperthermia (Wu et al., 1993). However, in sarcomas, IL-7 can stimulate the growth of cytotoxic T lymphocyes that can be utilized in adoptive immunotherapy. IL-7 activation of CD8+ from draining lymph nodes of mice injected with syngeneic fibrosarcomas enhances anti-tumour responsiveness when these lymphocytes were injected to mice with fibrosarcoma (Lynch et al., 1991). Furthermore, IL-7 producing glioma cells were not rejected in mice depleted of $CD8^+$ cells but were rejected in mice depleted of $CD4^+$ or $NK1.1^+$ cells, suggesting that $CD8^+$ T cells may play an important role in IL-7 induced tumor rejection (Jicha et al., 1991; Aoki et al., 1992).

However, to-date the extent of IL-7 and its receptor level of expression in solid tumours has not been fully elucidated. IL-7 R activation and the downstream signalling pathway in relation to solid tumour biology has been under-investigated. Furthermore, there has been no clear correlation between the level of expression of IL-7/IL-7R or their downstream signalling intermediates with tumour behaviour, size, grade of differentiation, rate of metastasis, nodal involvement as well as survival and prognosis in these cancers.

Perspectives and conclusions

IL-7 is a well established as a proliferative and trophic cytokine that induces the development and

proliferation of haematopoietic cells and malignancies. Recently, several publications have demonstrated the expression of IL-7 receptor in non-haematopietic neoplasms (Saito et al., 1997; Yamada et al., 1997). It is proposed that IL-7 might have some indirect effects on tumourigenesis via regulating some intracellular mechanisms, which might sensitise the cells to the effects of other cytokines and/or proliferative agents. The expression of IL-7 mRNA in some non-haematopoietic malignancies suggest the possibility for an autocrine growth pathway for IL-7. The production of IL-7 by some human solid tumours including colon and other cancers suggest a possible impact on the process of tumourigenesis. Furthermore, the detection of a functional IL-7 receptor in human solid malignancies also supports this concept. While the exact effects of IL-7 signalling activation is still unclear, the downstream signalling intermediates are upregulated in several human solid tumours including breast, lung, prostate, renal, ovarian, melanomas as well as head and neck tumours. This could be explained by the possibility of the occurrence of some changes in tumour microenvironment leading to changes in tumour development, behaviour and progression. Aberrant Jak – Stat pathways could indeed result in oncogenesis in some solid tumours. Better understanding of the mechanisms underlying these aberrant pathways in IL-7 signalling may lead to the development of novel cancer therapies based on interrupting key steps in these pathways. The relationship of IL-7 and solid tumours are still far from clear. Studies are currently underway to establish any relationship between IL-7 and breast cancer particularly in relation to tumour lymphangiogenesis and angiogenesis. Better understanding of the effects of IL-7 on endothelial and epithelial cell development, growth and differentiation as well as the mechanisms that control the activation of IL-7 signalling might have an important impact on oncogenesis. Therefore more studies are required to address this important issue.

References

Akbar A.N., Borthwick N.J., Wickremasinghe R.G., Panayoitidis P., Pilling D., Bofill M., Krajewski S., Reed J.C. and Salmon M. (1996). Interleukin-2 receptor common gamma-chain signaling cytokines regulate activated T cell apoptosis in response to growth factor withdrawal. selective induction of anti-apoptotic (bcl-2, bcl-xL) but not pro-apoptotic (bax, bcl-xS) gene expression. Eur. J. Immunol. 26, 294-299.

Alderson M. R., Sassenfeld H.M. and Widmer M. B. (1990). Interleukin 7 enhances cytolytic T lymphocyte generation and induces lymphokine-activated killer cells from human peripheral blood. J. Exp. Med. 172, 577-587.

Alderson M.R., Tough T.W., Ziegler S F. and Grabstein K.H. (1991). Interleukin 7 induces cytokine secretion and tumoricidal activity by human peripheral blood monocytes. J. Exp. Med. 173, 923-930.

Al-Rawi M., Mansel R .and Jiang W. (2002a). Interleukin-7 (IL-7) and IL-7 Receptor expression in breast cancer. Breast Cancer Res. Treat 76 Supplement 1, S144.

Al-Rawi M., Mansel R. and Jiang W. (2002b). Interleukin-7 is a putative lymphangiogenic factor in endothelial cells. Breast Cancer Res. Treat. 76 Supplement 1, S166.

Aoki T., Tashiro K., Miyatake S., Kinashi T., Nakano T., Oda Y., Kikuchi H. and Honjo T. (1992). Expression of murine interleukin 7 in a murine glioma cell line results in reduced tumorigenicity in vivo. Proc. Natl. Acad. Sci. USA 89, 3850-3854.

Appasamy P.M. (1993). Interleukin-7. Biology and potential clinical applications. Cancer Invest. 11, 487-499.

Appasamy P.M. (1999). Biological and clinical implications of interleukin-7 and lymphopoiesis. Cytokines Cell. Mol. Ther. 5, 25-39.

Baird A.M., Thomis D.C. and Berg L.J. (1998). T cell development and activation in Jak3-deficient mice. J. Leuk. Biol. 63, 669-677.

Benjamin D., Sharma V., Knobloch T.J., Armitage R.J., Dayton M.A. and Goodwin R.G. (1994). B-Cell Il-7 - human B-cell lines constitutively secrete Il-7 and express Il-7 receptors. J. Immunol. 152, 4749-4757.

Boise L.H., Minn A.J., June C.H., Lindsten T. and Thompson C.B. (1995). Growth factors can enhance lymphocyte survival without committing the cell to undergo cell division. Proc. Natl. Acad. Sci. USA 92, 5491-5495.

Bowman T., Garcia R., Turkson J. and Jove R. (2000). STATs in oncogenesis. Oncogene 19, 2474-2488.

Bromberg J.F., Horvath C.M., Wen Z., Schreiber R.D. and Darnell J.E. Jr. (1996). Transcriptionally active Stat1 is required for the antiproliferative effects of both interferon alpha and interferon gamma. Proc. Natl. Acad. Sci USA 93, 7673-7678.

Buard A., Vivo C., Monnet I., Boutin C., Pilatte Y. and Jaurand M.C. (1998). Human malignant mesothelioma cell growth. activation of janus kinase 2 and signal transducer and activator of transcription 1alpha for inhibition by interferon-gamma. Cancer Res. 58, 840-847.

Burow M.E., Weldon C.B., Collins-Burow B.M., Ramsey N., McKee A., Klippel A., McLachlan J.A., Clejan S. and Beckman B.S. (2000). Cross-talk between phosphatidylinositol 3-kinase and sphingomyelinase pathways as a mechanism for cell survival/death decisions. J. Biol. Chem. 275, 9628-9635.

Cance W.G. and Liu E.T. (1995). Protein kinases in human breast cancer. Breast Cancer Res Treat 35, 105-114.

Cao X., Tay A., Guy G.R. and Tan Y.H. (1996). Activation and association of Stat3 with Src in v-Src-transformed cell lines. Mol. Cell. Bio.l 16, 1595-603.

Cao X.Q., Shores E.W., Huli J., Anver M.R., Kelsall B.L., Russell S.M., Drago J., Noguchi M., Grinberg A., Bloom E.T., Paul W.E., Katz S.I., Love P.E. and Leonard W.J. (1995). Defective lymphoid development in mice lacking expression of the common cytokine receptor-gamma chain. Immunity 2, 223-238.

Carini C., McLane M.F., Mayer K.H. and Essex M. (1994). Dysregulation of interleukin-7 receptor may generate loss of cytotoxic T cell response in human immunodeficiency virus type 1 infection. Eur. J. Immunol. 24, 2927-2934.

Catlett-Falcone R., Dalton W.S. and Jove R. (1999). STAT proteins as novel targets for cancer therapy. Signal transducer an activator of transcription. Curr. Opin. Oncol. 11, 490-496.

Cayeux S., Beck C., Aicher A., Dorken B.and Blankenstein T. (1995). Tumor cells cotransfected with interleukin-7 and B7.1 genes induce CD25 and CD28 on tumor-infiltrating T lymphocytes and are strong

vaccines. Eur J Immunol 25, 2325-2331.

Chaturvedi P., Reddy M.V. and Reddy E.P. (1998). Src kinases and not JAKs activate STATs during IL-3 induced myeloid cell proliferation. Oncogene 16, 1749-1758.

Chung C.D., Liao J., Liu B., Rao X., Jay P., Berta P. and Shuai K. (1997). Specific inhibition of Stat3 signal transduction by PIAS3. Science 278, 1803-1805.

Coffer P.J., Jin J. and Woodgett J.R. (1998). Protein kinase B (c-Akt). a multifunctional mediator of phosphatidylinositol 3-kinase activation. Biochem. J. 335 , 1-13.

Coppola D. (2000). Molecular prognostic markers in pancreatic cancer. Cancer Control 7, 421-427.

Cosenza L., Gorgun G., Urbano A. and Foss F. (2002). Interleukin-7 receptor expression and activation in nonhaematopoietic neoplastic cell lines. Cell Signal 14, 317-325.

Costello R., Imbert J. and Olive D. (1993). Interleukin-7, a major T-lymphocyte cytokine. Eur. Cytokine Netw. 4, 253-262.

Dadi H., Ke S. and Roifman C.M. (1994). Activation of phosphatidylinositol-3 kinase by ligation of the Interleukin-7 Receptor Is Dependent on Protein-Tyrosine Kinase- Activity. Blood 84, 1579-1586.

Dalloul A., Laroche L., Bagot M., Mossalayi M.D., Fourcade C., Thacker D.J., Hogge D.E., Merle-Beral H., Debre P. and Schmitt C. (1992). Interleukin-7 is a growth factor for Sezary lymphoma cells. J. Clin. Invest. 90, 1054-1060.

Dhir R., Ni Z., Lou W., DeMiguel F., Grandis J.R. and Gao A.C. (2002). Stat3 activation in prostatic carcinomas. Prostate 51, 241-246.

Digel W., Schmid M., Heil G., Conrad P., Gillis S. and Porzsolt F. (1991). Human interleukin-7 induces proliferation of neoplastic cells from chronic lymphocytic leukemia and acute leukemias. Blood 78, 753-759.

Eder M., Ottmann O.G., Hansen-Hagge T.E., Bartram C.R., Falk S., Gillis S., Hoelzer D. and Ganser A. (1992). In vitro culture of common acute lymphoblastic leukemia blasts. effects of interleukin-3, interleukin-7, and accessory cells. Blood 79, 3274-3284.

Eves E.M., Xiong W., Bellacosa A., Kennedy S.G., Tsichlis P.N., Rosner M.R. and Hay N. (1998). Akt, a target of phosphatidylinositol 3-kinase, inhibits apoptosis in a differentiating neuronal cell line. Mol. Cell Biol. 18, 2143-2152.

Faltynek C.R., Wang S., Miller D., Young E., Tiberio L., Kross K., Kelley M. and Kloszewski E. (1992). Administration of human recombinant IL-7 to normal and irradiated mice increases the numbers of lymphocytes and some immature cells of the myeloid lineage. J. Immunol. 149, 1276-1282.

Fan S.J., Ma Y. X., Wang J.A., Yuan R.Q., Meng Q.H., Cao Y.J., Laterra J. J., Goldberg I.D. and Rosen E.M. (2000). The cytokine hepatocyte growth factor/scatter factor inhibits apoptosis and enhances DNA repair by a common mechanism involving signaling through phosphatidyl inositol 3 ' kinase. Oncogene 19, 2212-2223.

Fernandes A., Hamburger A.W. and Gerwin B.I. (1999). ErbB-2 kinase is required for constitutive stat 3 activation in malignant human lung epithelial cells. Int. J. Cancer 83, 564-570.

Foss H.D., Hummel M., Gottstein S., Ziemann K., Falini B., Herbst H. and Stein H. (1995). Frequent expression of IL-7 gene transcripts in tumor cells of classical Hodgkin's disease. Am. J. Pathol. 146, 33-39.

Foxwell B.M.J., Beadling C., Guschin D., Kerr I.and Cantrell D. (1995). Interleukin-7 can induce the activation of Jak-1, Jak-3 and Stat-5 Proteins in Murine T-Cells. Europ. J. Immunol. 25, 3041-3046.

Frishman J., Long, B., Knospe, W., Gregory S. and Plat J. (1993a). Genes for interleukin-7 are transcribed in leukemic-cell subsets of individuals with chronic lymphocytic-leukemia. J. Exp. Med. 177, 955-964.

Frishman J., Long B., Knospe W., Gregory S. and Plate J. (1993b). Genes for interleukin 7 are transcribed in leukemic cell subsets of individuals with chronic lymphocytic leukemia. J. Exp. Med. 177, 955-964.

Fujihashi K., McGhee J.R., Yamamoto M., Peschon J.J. and Kiyono H. (1997). An interleukin-7 internet for intestinal intraepithelial T cell development. knockout of ligand or receptor reveal differences in the immunodeficient state. Eur. J. Immunol. 27, 2133-2138.

Funk P.E., Stephan R.P. and Witte P.L. (1995). Vascular cell adhesion molecule 1-positive reticular cells express interleukin-7 and stem cell factor in the bone marrow. Blood 86, 2661-2671.

Garcia R. and Jove R. (1998). Activation of STAT transcription factors in oncogenic tyrosine kinase signaling. J. Biomed. Sci. 5, 79-85.

Garcia R., Bowman T.L., Niu G., Yu H., Minton S., Muro-Cacho, C. A., Cox C.E., Falcone R., Fairclough R., Parsons S., Laudano A., Gazit A., Levitzki A., Kraker A.and Jove R. (2001). Constitutive activation of Stat3 by the Src and JAK tyrosine kinases participates in growth regulation of human breast carcinoma cells. Oncogene 20, 2499-2513.

Garcia R., Yu C.L., Hudnall A., Catlett R., Nelson K.L., Smithgall T., Fujita D.J., Ethier S.P. and Jove R. (1997). Constitutive activation of Stat3 in fibroblasts transformed by diverse oncoproteins and in breast carcinoma cells. Cell Growth Differ 8, 1267-1276.

Gearing D.P., Druck T., Huebner K., Overhauser J., Gilbert D.J., Copeland N.G. and Jenkins N.A. (1993). The leukemia inhibitory factor receptor (LIFR) gene is located within a cluster of cytokine receptor loci on mouse chromosome 15 and human chromosome 5p12-p13. Genomics 18, 148-150.

Goodwin R.G., Friend D., Ziegler S.F., Jerzy R., Falk B. A., Gimpel S., Cosman D., Dower S. K., March C.J., Namen A. E. and Park L.S. (1990). Cloning of the human and murine interleukin-7 receptors - demonstration of a soluble form and homology to a new receptor superfamily. Cell 60, 941-951.

Goodwin R.G., Lupton S., Schmierer A., Hjerrild, K.J., Jerzy R., Clevenger W., Gillis S., Cosman D. and Namen A.E. (1989). Human interleukin-7 - molecular-cloning and growth-factor activity on human and murine B-lineage cells. Proc. Natl. Aacad. Sci. USA. 86, 302-306.

Gouilleux-Gruart V., Gouilleux F., Desaint C., Claisse J.F., Capiod J.C., Delobel J., Weber-Nordt R., Dusanter-Fourt I., Dreyfus F., Groner B. and Prin L. (1996). STAT-related transcription factors are constitutively activated in peripheral blood cells from acute leukemia patients. Blood 87, 1692-1697.

Grandis J.R., Drenning S.D., Chakraborty A., Zhou M.Y., Zeng Q., Pitt A.S.and Tweardy D.J. (1998). Requirement of Stat3 but not Stat1 activation for epidermal growth factor receptor- mediated cell growth In vitro. J. Clin. Invest. 102, 1385-1392.

Green A.R., Green V.L., White M.C. and Speirs V. (1997). Expression of cytokine messenger RNA in normal and neoplastic human breast tissue. identification of interleukin-8 as a potential regulatory factor in breast tumours. Int. J. Cancer 72, 937-941.

Greenlund A.C., Morales M.O., Viviano B.L., Yan H., Krolewski J.and Schreiber R.D. (1995). Stat recruitment by tyrosine-phosphorylated cytokine receptors. an ordered reversible affinity-driven process. Immunity 2, 677-687.

Grimley P.M., Fang H., Rui H., Petricoin E.F. 3rd, Ray S., Dong F., Fields K.H., Hu R., Zoon K.C., Audet S. and Beeler J. (1998). Prolonged STAT1 activation related to the growth arrest of malignant lymphoma cells by interferon-alpha. Blood 91, 3017-3027.

Gurniak C.B. and Berg L.J. (1996). Murine JAK3 is preferentially expressed in hematopoietic tissues and lymphocyte precursor cells. Blood 87, 3151-3160.

Haque S.J., Harbor P., Tabrizi M., Yi T. and Williams B.R. (1998). Protein-tyrosine phosphatase Shp-1 is a negative regulator of IL-4- and IL-13-dependent signal transduction. J. Biol. Chem. 273, 33893-33896.

Hasday J.D., Shah E.M. and Lieberman A.P. (1990). Macrophage tumor necrosis factor-alpha release is induced by contact with some tumors. J. Immunol. 145, 371-379.

Hausler P., Papoff G., Eramo A., Reif K., Cantrell D.A. and Ruberti G. (1998). Protection of CD95-mediated apoptosis by activation of phosphatidylinositide 3-kinase and protein kinase B. Eur. J. Immunol. 28, 57-69.

Heinrich P. C., Behrmann I., Muller-Newen G., Schaper F. and Graeve L. (1998). Interleukin-6-type cytokine signalling through the gp130/Jak/STAT pathway. Biochem J. 334 (Pt 2), 297-314.

Heufler C., Topar G., Grasseger A., Stanzl U., Koch F., Romani N., Namen A.E. and Schuler G. (1993). Interleukin 7 is produced by murine and human keratinocytes. J. Exp. Med. 178, 1109-1114.

Higuchi M., Asao H., Tanaka, N., Oda, K., Takeshita, T., Nakamura, M., VanSnick, J.and Sugamura K. (1996). Dispensability of Jak1 tyrosine kinase for interleukin-2- induced cell growth signaling in a human T cell line. Europ. Journal of Immunology 26, 1322-1327.

Hilton D.J., Richardson R.T., Alexander W.S., Viney E.M., Willson T. A., Sprigg N.S., Starr R., Nicholson S.E., Metcalf D. and Nicola N.A. (1998). Twenty proteins containing a C-terminal SOCS box form five structural classes. Proc. Natl. Acad. Sci. USA 95, 114-119.

Hoey T. and Grusby M.J. (1999). STATs as mediators of cytokine-induced responses. Adv. Immunol. 71, 145-162.

Hofmeister R., Khaled A.R., Benbernou N., Rajnavolgyi E., Muegge K. and Durum S.K. (1999). Interleukin-7. physiological roles and mechanisms of action. Cytok. Growth Factor Rev. 10, 41-60.

Horiguchi A., Oya M., Shimada T., Uchida A., Marumo K. and Murai M. (2002). Activation of signal transducer and activator of transcription 3 in renal cell carcinoma. A study of incidence and its association with pathological features and clinical outcome. J. Urol. 168, 762-765.

Huang M., Page C., Reynolds R.K. and Lin J. (2000). Constitutive activation of stat 3 oncogene product in human ovarian carcinoma cells. Gynecol. Oncol. 79, 67-73.

Hubbard S.R., Wei L., Ellis L. and Hendrickson W.A. (1994). Crystal structure of the tyrosine kinase domain of the human insulin receptor. Nature 372, 746-754.

Jiang D., Lenardo M.J. and Zuniga-Pflucker C. (1996). p53 prevents maturation to the $CD4^+CD8^+$ stage of thymocyte differentiation in the absence of T cell receptor rearrangement. J. Exp. Med. 183, 1923-1928.

Jicha D.L., Mule J.J. and Rosenberg S.A. (1991). Interleukin 7 generates antitumor cytotoxic T lymphocytes against murine sarcomas with efficacy in cellular adoptive immunotherapy. J. Exp. Med. 174, 1511-1515.

Jin L., Fuchs A., Schnitt S.J., Yao Y., Joseph A., Lamszus K., Park M., Goldberg I.D. and Rosen E.M. (1997). Expression of scatter factor and c-met receptor in benign and malignant breast tissue. Cancer 79, 749-760.

Johnston J.A., Bacon C.M., Finbloom D.S., Rees R.C., Kaplan D., Shibuya K., Ortaldo J.R., Gupta S., Chen Y. Q., Gir J.D. and Oshea J.J. (1995). Tyrosine phosphorylation and activation of Stat5, Stat3, and Janus kinases by interleukin-2 and interleukin-15. Proc. Natl. Acad. Sci. USA. 92, 8705-8709.

Kaplan D.H., Shankaran V., Dighe A.S., Stockert E., Aguet M., Old L.J. and Schreiber R.D. (1998). Demonstration of an interferon gamma-dependent tumor surveillance system in immunocompetent mice. Proc. Natl. Acad. Sci. USA 95, 7556-7561.

Kennedy S.G., Wagner A.J., Conzen S.D., Jordan J., Bellacosa A., Tsichlis P.N. and Hay N. (1997). The PI 3-kinase/Akt signaling pathway delivers an anti-apoptotic signal. Genes Dev. 11, 701-713.

Klingmuller U., Lorenz U., Cantley L.C., Neel B.G. and Lodish H.F. (1995). Specific recruitment of SH-PTP1 to the erythropoietin receptor causes inactivation of JAK2 and termination of proliferative signals. Cell 80, 729-738.

Komschlies K.L., Gregorio T.A., Gruys M.E., Back T.C., Faltynek C.R. and Wiltrout R.H. (1994). Administration of recombinant human IL-7 to mice alters the composition of B-lineage cells and T cell subsets, enhances T cell function, and induces regression of established metastases. J. Immunol. 152, 5776-5584.

Kondo M., Takeshita T., Higuchi M., Nakamura M., Sudo T., Nishikawa S.I. and Sugamura K. (1994). Functional Participation of the Il-2 receptor-gamma chain in Il-7 receptor complexes. Science 263, 1453-1454.

Kramer G., Steiner G.E., Paiha S., Handisurya A., Djavan B., Mallone R. and Marberger M. (2001). Human accessory cells activate fresh, normal, tumor-distant T lymphocytes but not tumor-infiltrating T lymphocytes to lyse autologous tumor cells in a primary cytotoxic T lymphocyte assay in renal cell carcinoma. Eur. Urol. 40, 427-433.

Kroemer R.T., Kroncke R., Gerdes J. and Richards W.G. (1998). Comparison of the 3D models of four different human IL-7 isoforms with human and murine IL-7. Protein Engineering 11, 31-40.

Lai K.S., Jin Y., Graha D.K., Witthuhn B.A., Ihle J.N. and Liu E.T. (1995). A kinase-deficient splice variant of the human JAK3 is expressed in hematopoietic and epithelial cancer cells. J. Biol. Chem. 270, 25028-25036.

Lai S.Y., Molden J. and Goldsmith M.A. (1997). Shared gamma(c) subunit within the human interleukin-7 receptor complex - A molecular basis for the pathogenesis of X-linked severe combined immunodeficiency. J. Clin. Invest. 99, 169-177.

Laky K., Lefrancois L., von Freeden-Jeffry U., Murray R. and Puddington L. (1998). The role of IL-7 in thymic and extrathymic development of TCR gamma delta cells. J. Immunol. 161, 707-713.

Leek R.D., Harris A.L. and Lewis C.E. (1994). Cytokine networks in solid human tumors. Regulation of angiogenesis. J. Leukoc. Biol. 56, 423-435.

Levy D. E. and Gilliland D.G. (2000). Divergent roles of STAT1 and STAT5 in malignancy as revealed by gene disruptions in mice. Oncogene 19, 2505-2510.

Lin J.X., Mietz J., Modi W.S., John S. and Leonard W. J. (1996). Cloning of human Stat5B. Reconstitution of interleukin-2-induced Stat5A and Stat5B DNA binding activity in COS-7 cells. J. Biol. Chem. 271, 10738-10744.

Lin J.X., Migone T.S., Tsang M., Friedmann M., Weatherbe J.A., Zhou L., Yamauchi A., Bloom E.T., Mietz J., John S. and Leonard W.J. (1995). The role of shared receptor motifs and Common Stat Proteins in the generation of cytokine pleiotropy and redundancy by

Il-2, Il-4, Il-7, Il-13, and Il-15. Immunity 2, 331-339.

Liu X., Robinson G.W., Gouilleux F., Groner B. and Hennighausen L. (1995). Cloning and expression of Stat5 and an additional homologue (Stat5b) involved in prolactin signal transduction in mouse mammary tissue. Proc. Natl. Acad. Sci. USA 92, 8831-8835.

Liu X., Robinson G.W., Wagner K.U., Garrett L., Wynshaw-Boris A. and Hennighausen L. (1997). Stat5a is mandatory for adult mammary gland development and lactogenesis. Genes Dev. 11, 179-186.

Lynch D.H., Namen A.E. and Miller R.E. (1991). In vivo evaluation of the effects of interleukins 2, 4 and 7 on enhancing the immunotherapeutic efficacy of anti-tumor cytotoxic T lymphocytes. Eur. J. Immunol. 21, 2977-2985.

Maeurer M.J., Walter W., Martin, D., Zitvogel L., Elder, E., Storkus W. and Lotze M.T. (1997). Interleukin-7 (IL-7) in colorectal cancer. IL-7 is produced by tissues from colorectal cancer and promotes preferential expansion of tumour infiltrating lymphocytes. Scand. J. Immunol. 45, 182-192.

Maraskovsky E., Teepe M., Morrissey P.J., Braddy S., Miller R.E., Lynch D.H. and Peschon J.J. (1996). Impaired survival and proliferation in IL-7 receptor-deficient peripheral T cells. J. Immunol. 157, 5315-5323.

Matsumoto A., Masuhara M., Mitsui K., Yokouchi M., Ohtsubo M., Misawa H., Miyajima A.and Yoshimura A. (1997). CIS, a cytokine inducible SH2 protein, is a target of the JAK-STAT5 pathway and modulates STAT5 activation. Blood 89, 3148-3154.

Matsumoto A., Seki Y., Kubo M., Ohtsuka S., Suzuki A., Hayashi I., Tsuji K., Nakahata T., Okabe M., Yamada S. and Yoshimura A. (1999). Suppression of STAT5 functions in liver, mammary glands, and T cells in cytokine-inducible SH2-containing protein 1 transgenic mice. Mol. Cell. Biol 19, 6396-6407.

Mattei S., Colombo M.P., Melani C., Silvani A., Parmiani G. and Herlyn M. (1994). Expression of cytokine/growth factors and their receptors in human melanoma and melanocytes. Int. J. Cancer 56, 853-857.

Migone T.S., Lin J.X., Cereseto A., Mullo J.C., O'Shea J.J., Franchini G. and Leonard W.J. (1995). Constitutively activated Jak-STAT pathway in T cells transformed with HTLV-I. Science 269, 79-81.

Miller A.R., McBride W.H., Dubinett S.M., Dougherty G.J., Thacker J.D., Shau H., Kohn D.B., Moen R.C., Walker M.J. and Chiu R. (1993). Transduction of human melanoma cell lines with the human interleukin-7 gene using retroviral-mediated gene transfer. comparison of immunologic properties with interleukin-2. Blood 82, 3686-3694.

Miyazaki T., Takaoka A., Nogueira L., Dikic I., Fujii H., Tsujino S., Mitani Y., Maeda M., Schlessinger J. and Taniguchi T. (1998). Pyk2 is a downstream mediator of the IL-2 receptor-coupled Jak signaling pathway. Genes Dev. 2, 770-775.

Morrissey P.J., Conlon P., Braddy S., Williams D.E., Namen A.E. and Mochizuki D.Y. (1991a). Administration of IL-7 to mice with cyclophosphamide-induced lymphopenia accelerates lymphocyte repopulation. J. Immunol. 146, 1547-1552.

Morrissey P.J., Conlon P., Charrier K., Braddy S., Alpert A., Williams D., Namen A.E. and Mochizuki D. (1991b). Administration of IL-7 to normal mice stimulates B-lymphopoiesis and peripheral lymphadenopathy. J. Immunol. 147, 561-568.

Murakami M., Narazaki M., Hibi M., Yawata H., Yasukawa K., Hamaguchi M., Taga T. and Kishimoto T. (1991). Critical cytoplasmic region of the interleukin-6 signal transducer Gp130 is conserved in the cytokine receptor family. Proc. Nat. Acad. Sci. USA 88, 11349-11353.

Namen A.E., Lupton S., Hjerrild K., Wignall J., Mochizuki D.Y., Schmierer A., Mosley B., March C.J., Urdal D., Gillis S., Cosman D. and Goodwin R.G. (1988a). Stimulation of B-Cell progenitors by cloned murine interleukin- 7. Nature 333, 571-573.

Namen A.E., Schmierer A.E., March C.J., Overell R W., Park L.S., Urdal D.L. and Mochizuki D.Y. (1988b). B cell precursor growth-promoting activity. Purification and characterization of a growth factor active on lymphocyte precursors. J. Exp. Med. 167, 988-1002.

Noguchi M., Nakamura Y., Russell S.M., Ziegler S.F., Tsang M., Cao X.Q .and Leonard W.J. (1993). Interleukin-2 teceptor gamma-chain - a functional component of the interleukin-7 receptor. Science 262, 1877-1880.

Nosaka T., Vandeursen J.M.A., Tripp R.A., Thierfelder W.E., Witthuhn B.A., McMickle A.P., Doherty P.C., Grosveld G.C. and Ihle J.N. (1995). Defective lymphoid development in mice lacking Jak3. Science 270, 800-802.

Oka M., Hirose K., Iizuka N., Aoyagi K., Yamamoto K., Abe T., Hazama S. and Suzuki T. (1995). Cytokine mRNA expression patterns in human esophageal cancer cell lines. J. Interferon Cytokine Res. 15, 1005-1009.

Ortmann R.A., Cheng T., Visconti R., Frucht D.M. and O'Shea J.J. (2000). Janus kinases and signal transducers and activators of transcription. their roles in cytokine signaling, development and immunoregulation. Arthritis Res 2, 16-32.

Page T.H., Lali F.V. and Foxwell B.M.J. (1995). Interleukin-7 Activates P56(Lck) and P59(Fyn), 2 Tyrosine kinases associated with the p90 interleukin-7 receptor in primary human T-cells. Eur. J. Immunol. 25, 2956-2960.

Paleri V., Pulimood A., Davie G.R. and Birchall M.A. (2001). Interleukins 7 and 12 are expressed in head and neck squamous cancer. Clin. Otolaryngol. 26, 302-306.

Pansky A., Hildebrand P., Fasler-Kan E., Baselgia L., Ketterer S., Beglinger C. and Heim M.H. (2000). Defective Jak-STAT signal transduction pathway in melanoma cells resistant to growth inhibition by interferon-alpha. Int. J. Cancer 85, 720-725.

Park L.S., Friend D.J., Schmierer A.E., Dower S.K. and Namen A.E. (1990). Murine interleukin 7 (IL-7) receptor. Characterization on an IL-7-dependent cell line. J. Exp. Med. 171, 1073-1089.

Pernis A., Gupta S., Yopp J., Garfein E., Kashleva H., Schindler C. and Rothman P. (1995). Gamma-chain-associated cytokine receptors signal through distinct transducing factors. J. Biol. Chem. 270, 14517-14522.

Pezet A., Favre H., Kelly P.A. and Edery M. (1999). Inhibition and restoration of prolactin signal transduction by suppressors of cytokine signaling. J. Biol. Chem. 274, 24497-24502.

Pivniouk V., Tsitsikov E., Swinton P., Rathbun G., Alt F.W. and Geha R.S. (1998). Impaired viability and profound block in thymocyte development in mice lacking the adaptor protein SLP-76. Cell 94, 229-238.

Potocnik A.J., Nielsen P.J. and Eichmann K. (1994). In vitro generation of lymphoid precursors from embryonic stem cells. EMBO J. 13, 5274-5283.

Qin J.Z., Zhang C.L., Kamarashev J., Dummer R., Burg G. and Dobbeling U. (2001). Interleukin-7 and interleukin-15 regulate the expression of the bcl-2 and c-myb genes in cutaneous T-cell lymphoma cells. Blood 98, 2778-2783.

Ray R.J., Furlonger C., Williams D.E. and Paige C.J. (1996). Characterization of thymic stromal-derived lymphopoietin (TSLP) in murine B cell development in vitro. Eur. J. Immunol. 26, 10-16.

Rich B.E., Campos-Torres J., Tepper R.I., Moreadith R.W. and Leder P. (1993). Cutaneous lymphoproliferation and lymphomas in interleukin 7 transgenic mice. J. Exp. Med. 177, 305-316.

Rosenthal L.A., Winestock K.D. and Finbloom D.S. (1997). IL-2 and IL-7 induce heterodimerization of STAT5 isoforms in human peripheral blood T lymphoblasts. Cell. Immunol. 181, 172-181.

Rowan S. and Fisher D.E. (1997). Mechanisms of apoptotic cell death. Leukemia 11, 457-465.

Saito S., Harada N., Ishii N., Morii T., Sakakura S., Enomoto M., Umekage H., Nishikawa K., Narita N., Nakamura M., Sugamura K. and Morikawa H. (1997). Functional expression on human trophoblasts of interleukin 4 and interleukin 7 receptor complexes with a common gamma chain. Biochem. Biophys. Res. Commun. 231, 429-434.

Sartor C.I., Dziubinski M.L., Yu C.L., Jove R. and Ethier S.P. (1997). Role of epidermal growth factor receptor and STAT-3 activation in autonomous proliferation of SUM-102PT human breast cancer cells. Cancer Res. 57, 978-987.

Seckinger P. and Fougereau M. (1994). Activation of Src family kinases in human Pre-B cells by Il-7. J. Immunol. 153, 97-109.

Sharma S., Miller P.W., Stolina M., Zhu L., Huang M., Paul R.W. and Dubinett S.M. (1997). Multicomponent gene therapy vaccines for lung cancer. Effective eradication of established murine tumors in vivo with interleukin-7/herpes simplex thymidine kinase-transduced autologous tumor and ex vivo activated dendritic cells. Gene Ther 4, 1361-1370.

Sharma S., Wang, J., Huang, M., Paul, R. W., Lee, P., McBride, W. H., Economou, J. S., Roth, M. D., Kiertscher, S. M.and Dubinett, S. M. (1996). Interleukin-7 gene transfer in non-small-cell lung cancer decreases tumor proliferation, modifies cell surface molecule expression, and enhances antitumor reactivity. Cancer Gene Ther. 3, 302-313.

Sica D., Rayman P., Stanley J., Edinger M., Tubbs R. R., Klein E., Bukowski R. and Finke J.H. (1993). Interleukin 7 enhances the proliferation and effector function of tumor-infiltrating lymphocytes from renal-cell carcinoma. Int. J. Cancer 53, 941-947.

Silva M.R., Hoffman R., Srour E.F. and Ascensao J.L. (1994). Generation of human natural killer cells from immature progenitors does not require marrow stromal cells. Blood 84, 841-846.

Soloff R.S., Wang T.G., Dempsey D., Jennings S.R., Wolcott R.M. and Chervenak R. (1997). Interleukin 7 induces TCR gene rearrangement in adult marrow-resident murine precursor T cells. Mol. Immunol. 34, 453-462.

Sun M., Paciga J.E., Feldman R.I., Yuan Z.Q., Coppola D., Lu, Y. Y., Shelley S.A., Nicosia S.V. and Cheng J.Q. (2001). Phosphatidylinositol-3-OH kinase (PI3K)/AKT2, activated in breast cancer, regulates and is induced by estrogen receptor alpha (ER alpha) via interaction between ER alpha and PI3K. Cancer Res. 61, 5985-5991.

Sweeney E.B., Foss F.M., Murphy J.R. and VanderSpek J.C. (1998). Interleukin 7 (IL-7) receptor-specific cell killing by DAB389 IL-7. A novel agent for the elimination of IL-7 receptor positive cells. Bioconjug. Chem. 9, 201-207.

Takakuwa T., Nomura S., Matsuzuka F., Inoue H. and Aozasa K. (2000). Expression of interleukin-7 and its receptor in thyroid lymphoma. Lab. Invest. 80, 1483-1490.

Takeshita T., Arita T., Asao H., Tanaka N., Higuchi M., Kuroda H., Kaneko K., Munakata H., Endo Y., Fujita T. and Sugamura K. (1996). Cloning of a novel signal-transducing adaptor molecule containing an SH3 domain and ITAM. Biochem. Biophys. Res. Commun. 225, 1035-1039.

Takeshita T., Arita, T., Higuchi, M., Asao H., Endo K., Kuroda H., Tanaka N., Murata K., Ishii N. and Sugamura K. (1997). STAM, signal transducing adaptor molecule, is associated with Janus kinases and involved in signaling for cell growth and c- myc induction. Immunity 6, 449-457.

Takeuchi T., Yamanouchi H., Yue Q. and Ohtsuki Y. (1998). Epithelial component of lymphoid stroma-rich Warthin's tumour expresses interleukin (IL)-7. Histopathology 32, 383-384.

Talmadge J.E., Jackson J.D., Kelsey L., Borgeson C.D., Faltynek C. and Perry G.A. (1993). T-cell reconstitution by molecular, phenotypic, and functional analysis in the thymus, bone marrow, spleen, and blood following split-dose polychemotherapy and therapeutic activity for metastatic breast cancer in mice. J. Immunother. 14, 258-268.

Taniguchi T. and Minami Y. (1993). The IL-2/IL-2 receptor system. A current overview. Cell 73, 5-8.

Thomis D.C., Gurniak C.B., Tivol E., Sharpe A.H. and Berg L.J. (1995). Defects in B-Lymphocyte maturation and T-lymphocyte activation in mice lacking Jak3. Science 270, 794-797.

Toker A. and Cantley L.C. (1997). Signalling through the lipid products of phosphoinositide-3-OH kinase. Nature 387, 673-676.

Touw I., Pouwels K., van Agthoven T., van Gurp R., Budel L., Hoogerbrugge H., Delwel R., Goodwi R., Namen A. and Lowenberg B. (1990). Interleukin-7 is a growth factor of precursor B and T acute lymphoblastic leukemia. Blood 75, 2097-2101.

Trinder P., Seitzer U., Gerdes J., Seliger B. and Maeurer M. (1999). Constitutive and IFN-gamma regulated expression of IL-7 and IL-15 in human renal cell cancer. Int. J. Oncol. 14, 23-31.

Trumper L., Jung W., Dahl G., Diehl V., Gause A. and Pfreundschuh M. (1994). Interleukin-7, interleukin-8, soluble TNF receptor, and p53 protein levels are elevated in the serum of patients with Hodgkin's disease. Ann. Oncol. 5 Suppl 1, 93-96.

van der Plas D.C., Smiers F., Pouwels K., Hoefsloot L.H., Lowenberg B. and Touw I.P. (1996). Interleukin-7 signaling in human B cell precursor acute lymphoblastic leukemia cells and murine BAF3 cells involves activation of STAT1 and STAT5 mediated via the interleukin-7 receptor alpha chain. Leukemia 10, 1317-1325.

Vanhaesebroeck B., Leevers S.J., Panayotou G. and Waterfield M.D. (1997). Phosphoinositide 3-kinases. a conserved family of signal transducers. Trends Biochem. Sci. 22, 267-272.

Venkitaraman A.R.and Cowling R.J. (1992). Interleukin-7 receptor functions by recruiting the tyrosine kinase P59(Fyn) through a segment of its cytoplasmic tail. Proc. Nat. Acad. Sci. USA 89, 12083-12087.

von Freeden-Jeffry U., Vieira P., Lucian L.A., McNei T., Burdach S.E. and Murray R. (1995). Lymphopenia in interleukin (IL)-7 gene-deleted mice identifies IL-7 as a nonredundant cytokine. J. Exp. Med. 181, 1519-1526.

Watanabe M., Ueno Y., Yajima T., Iwao Y., Tsuchiya M., Ishikawa H., Aiso S., Hibi T. and Ishii H. (1995). Interleukin-7 is produced by human intestinal epithelial-cells and regulates the proliferation of intestinal mucosal lymphocytes. J. Clin. Investigation 95, 2945-2953.

Watson C.J.and Miller W.R. (1995). Elevated levels of members of the STAT family of transcription factors in breast carcinoma nuclear extracts. Br. J. Cancer 71, 840-844.

Weber-Nordt R. M., Egen, C., Wehinger, J., Ludwig, W., Gouilleux-Gruart, V., Mertelsmann, R.and Finke J. (1996). Constitutive

activation of STAT proteins in primary lymphoid and myeloid leukemia cells and in Epstein-Barr virus (EBV)-related lymphoma cell lines. Blood 88, 809-816.

Wen X., Lin H.H., Shih H.M., Kung, H.J.and Ann D.K. (1999). Kinase activation of the non-receptor tyrosine kinase Etk/BMX alone is sufficient to transactivate STAT-mediated gene expression in salivary and lung epithelial cells. J. Biol. Chem. 274, 38204-38210.

Wiles M.V., Ruiz P. and Imhof B.A. (1992). Interleukin-7 expression during mouse thymus development. Eur. J. Immunol. 22, 1037-1042.

Wong B.R., Besser D., Kim N., Arron J.R., Vologodskaia M., Hanafusa H. and Choi Y. (1999). TRANCE, a TNF family member, activates Akt/PKB through a signaling complex involving TRAF6 and c-Src. Mol. Cell 4, 1041-1049.

Wu B., Shen R.N., Wang W.X., Broxmeyer H.E. and Lu L. (1993). Antitumor effect of interleukin 7 in combination with local hyperthermia in mice bearing B16a melanoma cells. Stem Cells 11, 412-421.

Yamada K., Shimaoka, M., Nagayama, K., Hiroi, T., Kiyono H. and Honda T. (1997). Bacterial invasion induces interleukin-7 receptor expression in colonic epithelial cell line, T84. Eur. J. Immunol. 3456-3460.

Yamashita J., Ogawa M., Yamashita S., Nomura K., Kuramoto M., Saishoji T. and Shin S. (1994). Immunoreactive hepatocyte growth factor is a strong and independent predictor of recurrence and survival in human breast cancer. Cancer Res. 54, 1630-1633.

Ye B.H., Cattoretti G., Shen Q., Zhang J., Hawe N., de Waard R., Leung C., Nouri-Shirazi M., Orazi A., Chaganti R.S., Rothman, P., Stall A.M., Pandolfi P. P.and Dalla-Favera R. (1997). The BCL-6 proto-oncogene controls germinal-centre formation and Th2-type inflammation. Nat. Genet. 16, 161-170.

Yoshimura A., Ohkubo T., Kiguchi T., Jenkins N.A., Gilbert D.J., Copeland N.G., Hara T. and Miyajima A. (1995). A novel cytokine-inducible gene CIS encodes an SH2-containing protein that binds to tyrosine-phosphorylated interleukin 3 and erythropoietin receptors. EMBO J. 14, 2816-2826.

Yu C.L., Meyer D.J., Campbell G.S., Larner A.C., Carter-Su C., Schwartz J. and Jove R. (1995). Enhanced DNA-binding activity of a Stat3-related protein in cells transformed by the Src oncoprotein. Science 269, 81-83.

Zeng Y.X., Takahashi H., Shibata M. and Hirokawa K. (1994). Jak3 janus linase is involved in interleukin-7 signal pathway. FEBS Lett. 353, 289-293.

Zhang Q., Nowak I., Vonderheid E.C., Rook A.H., Kadin M.E., Nowell P.C., Shaw L.M.and Wasik M.A. (1996). Activation of Jak/STAT proteins involved in signal transduction pathway mediated by receptor for interleukin 2 in malignant T lymphocytes derived from cutaneous anaplastic large T-cell lymphoma and Sezary syndrome. Proc. Natl. Acad. Sci. USA 93, 9148-9153.

Zong C., Yan R., August A., Darnell J.E., Jr. and Hanafusa H. (1996). Unique signal transduction of Eyk. constitutive stimulation of the JAK-STAT pathway by an oncogenic receptor-type tyrosine kinase. EMBO J 15, 4515-4525.

Zong C.S., Zeng L., Jiang Y., Sadowski H.B. and Wang L.H. (1998). Stat3 plays an important role in oncogenic Ros- and insulin-like growth factor I receptor-induced anchorage-independent growth. J Biol Chem 273, 28065-28072.

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