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Tyrosine kinase 2 (TYK2) in cytokine signalling and host immunity

Birgit Strobl[1], Dagmar Stoiber[2,3], Veronika Sexl[4], Mathias Mueller[1,5]

[1] Institute of Animal Breeding and Genetics, University of Veterinary Medicine Vienna, Veterinaerplatz 1, 1210 Vienna, Austria, [2]Ludwig Boltzmann Institute for Cancer Research (LBI-CR), Waehringerstrasse 13A, 1090 Vienna, Austria, [3]Institute of Pharmacology, Medical University of Vienna, Waehringerstrasse 13A, 1090 Vienna, Austria, [4]Institute of Pharmacology and Toxicology, University of Veterinary Medicine Vienna, Veterinaerplatz 1, 1210 Vienna, Austria, [5]Biomodels Austria, University of Veterinary Medicine Vienna, Veterinaerplatz 1, 1210 Vienna, Austria

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1. ABSTRACT

The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) signal transduction pathway is essential to transmit signals from transmembrane receptors to the nucleus in order to alter gene expression programs and to respond to extracellular cues. Tyrosine kinase 2 (TYK2) was the first member of the JAK family that was identified within a screen for molecules complementing human cell lines mutant for interferon (IFN) responses. During the last decades biochemical studies and gene-targeted mice uncovered the crucial role of TYK2 in immunity. Tyk2-deficient mice are viable and fertile but display multiple immunological defects, most prominently high sensitivity to infections and defective tumour surveillance. In contrast, absence of TYK2 results in increased resistance against allergic, autoimmune and inflammatory diseases. In support of these data, the only patient with TYK2 deficiency described so far displays high serum immunoglobulin E (IgE) levels and increased sensitivity to infectious diseases. Furthermore, numerous genome-wide association studies in humans propose a link between TYK2 genetic variants and several autoimmune diseases, inflammatory diseases and tumours. Thus, TYK2 appears as an attractive target for therapeutic intervention. Future work will be required to further delineate structure-function relationships and to fully understand the involvement of TYK2 in immune regulatory networks.

2. INTRODUCTION

Tyrosine kinase 2 (TYK2) has been originally identified and cloned from a lymphoid cDNA screen using the c-fms kinase domain as a probe (1, 2). The involvement of TYK2 in cytokine signalling has been discovered by its ability to complement defects in a mutant human cell line that is unresponsive to interferon (IFN)alpha/beta (3). A similar approach led to the identification of other Janus kinase (JAK) family members and the signal transducers and activators of transcription (STATs) as major components of signal transduction in response to many cytokines, and the JAK/STAT pathway as a paradigm for cytokine signalling (4). Four JAKs (JAK1, JAK2, JAK3 and TYK2) and seven STATs (STAT1-4, STAT5a, STAT5b and STAT6) exist in mammalian cells. JAKs are receptor-associated tyrosine kinases that get activated upon ligand binding to the extracellular domain of the respective receptor complex. JAKs auto- and/or transphosphorylate and phosphorylate receptor chains, which become docking sites for STATs. JAKs then phosphorylate recruited STAT homo- and/or heterodimers, which subsequently translocate to the nucleus and induce transcription of target genes. JAKs specifically associate with different cytokine receptors and act either alone or in combination with other

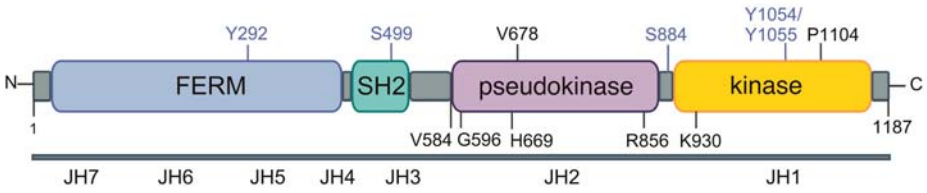

Figure 1. Schematic representation of structural and functional domains of the TYK2 protein. Seven JAK homology domains (JH1-JH7) and 4 structural domains (kinase, pseudokinase, SH2 and FERM domain) have been identified. Tyrosine (Y) and serine (S) residues that have been reported to undergo phosphorylation are indicated in blue, amino acids that affect kinase activity when mutated are in black. Amino acid numbering is according to the human TYK2 protein. See text for details.

JAK family members. Interestingly, TYK2 is activated in combination with JAK1 and/or JAK2 but not with JAK3. Depending on the cytokine and the cell type, one or up to all seven different STATs can be activated. However, specific STAT complexes dominate the biological responses to a given cytokine and the role of additionally activated STATs is often unknown (5, 6).

Most of the early studies addressing molecular functions of TYK2 have been performed in a human fibrosarcoma cell line lacking TYK2 (U1A) and derivatives thereof (3). *Tyk2*-deficient mice have been generated by three groups using different targeting strategies, i.e. replacement of the exons encoding part of JH7, JH6-JH5 and part of JH4 (7) or of the first coding exon (8) by a neomycin cassette, or deletion of 3 exons encompassing the 5' non-translated region and the start codon (9). The B10.Q/J (B10.D1-H2^{q}/SgJ) mouse strain, a naturally occurring *Tyk2* mutant mouse strain, represents an additional mouse model to study TYK2 functions (10). The B10.Q/J *Tyk2* gene contains a single point mutation (G2538A) resulting in a non-conserved amino acid exchange in the pseudokinase domain (E775K). It is not yet clear whether TYK2 protein is absent (10) or just inactive (11) in these mice. *Tyk2*-deficient mice are viable and fertile, but show multiple and striking immunological phenotypes. This is in contrast to the embryonic and perinatal lethal phenotype of *Jak2*- and *Jak1*-deficient mice, as these two JAKs are crucial for signalling of cytokines involved in erythropoietic and neuronal development, respectively (12, 13). *Jak3*-deficient mice are viable but suffer from severe combined immunodeficiency (SCID) (14, 15), which is due to the essential role of JAK3 in signalling of cytokines essential during haematopoiesis and T cell development.

In this review we summarize the current knowledge about the role of TYK2 in cytokine signalling, the consequences of *Tyk2* deficiency in mice and humans and we discuss the challenges for future work.

3. TYK2 PROTEIN STRUCTURE AND REGULATION

The *Tyk2* gene is located on chromosome 9 in mice and on chromosome 19 in humans (1, 10). *Tyk2* is ubiquitously expressed, although the expression level differs between cell types (http://biogps.gnf.org). The TYK2 protein has around 1200 amino acids and a theoretical molecular weight of approximately 130 kDa (Figure 1). JAKs are multi-domain proteins that share seven homology regions (JH1-JH7). They contain tandem kinase domains, one is an active kinase (carboxyl-terminal JH1) and the other adjacent domain is catalytically inactive and referred to as kinase-like or pseudokinase domain (JH2). Within JH1, conserved dual tyrosine residues are located in the so-called activation-loop, a general characteristic of protein tyrosine kinases. Auto- and/or transphosphorylation by other JAKs is thought to induce conformational changes that usually positively regulate kinase activity and facilitate substrate binding (6). In human TYK2 mutation of these adjacent tyrosine residues (Y1054/Y1055) to phenylalanine does not impair basal catalytic activity of the kinase but completely abolishes ligand-induced activation (16). Lysine 930 (K930) constitutes the ATP binding site of the kinase domain and, consequently, mutation of this site completely abrogates enzyme activity (16). The pseudokinase domain exerts critical regulatory functions (6). Deletion or specific point mutations (V584D, G596V, H669P, R856G) in the pseudokinase domain of TYK2 abolish catalytic activity (17, 18). In contrast, mutation of valine 678 to phenylalanine (V678F) increases TYK2 kinase activity (19, 20).

The N-terminal half of JAK proteins is most divergent and contains a src-homology 2 (SH2) domain (JH3 and part of JH4) with unknown function and a four-point-one, ezrin, radixin, moesin (FERM) homology domain (part of JH4 and JH5-JH7). The FERM domain is a protein-protein interaction domain and is implicated in JAK-receptor interaction and specificity and, at least in the case of JAK2, can regulate kinase activity (6). Extensive analysis of TYK2 deletion mutants using *in vitro* binding assays identified the major interaction surface of TYK2 with IFNalpha/beta receptor chain 1 (IFNAR1) within the amino acids 21-221 (part of JH6 and JH7), whereas JH3-5 contribute to the stable assembly of TYK2-IFNAR1 complexes (21). Apart from the dual tyrosine residues in the kinase domain, additional phosphorylation sites have been identified by phosphoproteome mapping in human TYK2, namely one tyrosine (Y292) and two serine (S499 and S884) residues (22-26). Potential regulatory functions of these sites remain to be investigated. There are no complete three-dimensional structures available for the JAKs, but the crystal structure of the kinase domains of all JAKs has been solved in their active, inhibitor-bound state (27-30). Theoretical models for the structures of the tandem

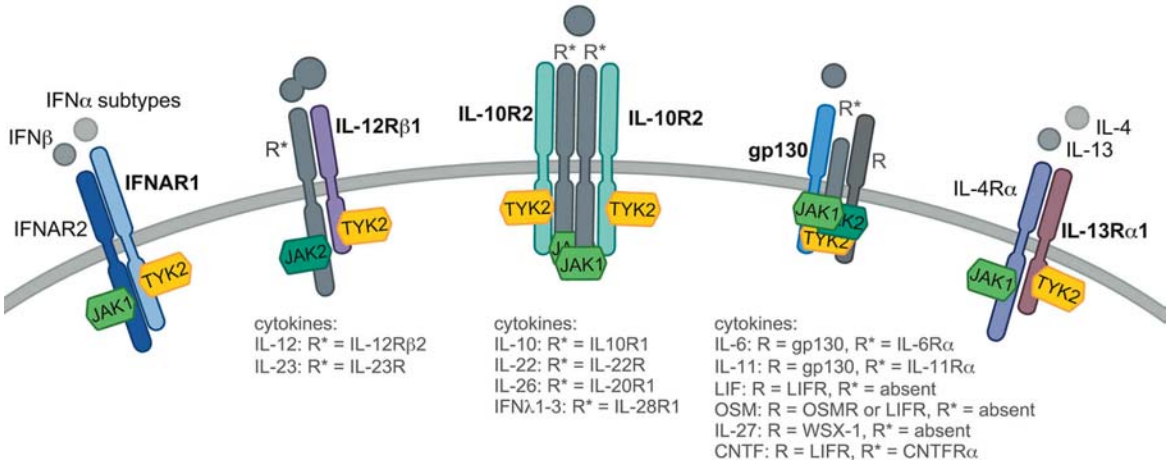

Figure 2. Cytokines and receptor complexes that engage TYK2 for signalling. Several of these cytokines share common receptor chains engaging TYK2 in combination with other receptor chains (R*/R) that confers specificity and are bound by either JAK1 or JAK2. Cytokines and their respective R*/R are listed. IL-4 also signals via the IL-4/gammac complex that does not utilize TYK2. IL-26 is conserved among most vertebrates, but has not been found in mice. It is still unknown whether JAK1 or JAK2 binds the second IL-26 receptor chain (IL-20R1). *Ifnlamda1* is a pseudogene in mice. See text for details.

kinase domains and the full-length protein have been presented for JAK2 (31, 32).

A number of tyrosine phosphatases can inactivate JAKs (33). The SH2 domain-containing phosphatase SHP-1 has been shown to associate with TYK2 (34, 35) and stable transfection of SHP-1 in lymphoblast cell lines promotes TYK2 protein degradation (36). A substrate-trapping mutant of the tyrosine phosphatase PTB1B interacts with JAK2 and TYK2 and PTB1B negatively regulates IFNalpha and IFNgamma signalling (37). The receptor tyrosine phosphatase CD45 can suppress phosphorylation of JAKs1-3 and TYK2 (38), however, the physiological significance of CD45-mediated downregulation of JAK activity needs to be further investigated. JAK activity is also inhibited by members of the suppressor of cytokine signalling (SOCS) protein family (39). SOCS proteins inhibit JAK/STAT signalling either by direct inhibition of JAK activity (e.g. SOCS1), recruitment to the receptor cytoplasmic domain followed by inhibition of JAK activity (e.g. SOCS3), or by competition with STATs for binding to receptor phosphotyrosine motifs (e.g. SOCS2). In addition, SOCS proteins can also target JAKs for proteasomal degradation which is mediated by the interaction of the SOCS box motif with an E3 ubiquitin-ligase complex. Among the SOCS proteins, SOCS1 and SOCS3 can interact with TYK2 (40-42).

Interestingly, several viruses specifically target TYK2 protein and/or activity by as yet unknown mechanisms. The Human Papilloma Virus-18 E6 protein and the Epstein-Barr Virus LMP-1 protein physically associate with TYK2 and impair STAT1/2 activation in response to IFNalpha/beta (43, 44). Sendai virus infection and transfection of the complete Hepatitis Delta Virus genome block TYK2 phosphorylation in response to IFNalpha/beta without affecting JAK1 activity (45, 46).

4. TYK2 IN CYTOKINE SIGNALLING

Type I and type II cytokine receptors are a structurally distinct class of receptors that lack intrinsic kinase activity and specifically associate with certain JAKs. Different cytokines use specific combinations of receptor chains and, consequently, activate different combinations of JAKs. TYK2 associates with IFNAR1, IL-12Rbeta1, IL-10R2, gp130 and IL-13Ralpha1 receptor chains which are utilized by a large number of different cytokines (Figure 2), the respective second receptor chain associates with JAK1 and/or JAK2.

4.1. Type I IFN

The type I IFN family includes more than 20 members, most prominently several IFNalpha subtypes and IFNbeta (47, 48). Type I IFNs signal through IFNAR1 and IFNAR2, which associate with TYK2 and JAK1, respectively. STAT1 and STAT2 are the major signal transducing STATs in response to type I IFNs (4, 49). Nevertheless, also all other STATs can be activated and contribute to responses in a cell type-specific manner (50). Mutant human cell lines lacking TYK2 are completely unresponsive to IFNalpha and show reduced responses to IFNbeta (3). This seems to be largely due to a dramatic reduction of IFNAR1 surface expression and the consequent loss of high-affinity IFNalpha binding in the absence of TYK2 (51, 52). Importantly, this is different in murine cells. Fibroblasts and macrophages derived from *Tyk2*-deficient mice show normal IFNAR1 surface expression and only partially impaired IFNalpha/beta signalling (7-9). In fact, strong effects of *Tyk2* deficiency on IFNalpha/beta responses are only observed at low-dose of IFNs in murine fibroblasts and macrophages as monitored by antiviral activity and MHC Class I induction, respectively (8). Recent studies identified a linear endocytic motif in the cytoplasmic domain of human IFNAR1 (53). Binding of TYK2 to this motif prevents ligand-independent

IFNAR1 internalisation and thus ensures maintenance of receptor surface expression. Importantly, this motif is absent in murine IFNAR1. In human cells, kinase-inactive TYK2 and deletion mutants lacking either the kinase or the pseudokinase domain restore IFNAR1 surface expression (52). Nevertheless, the pseudokinase domain is involved in the establishment of high-affinity IFNalpha receptor complexes (18). In contrast to the basal IFNAR1 surface expression, TYK2 kinase activity contributes to efficient IFNAR1 ubiquitination and degradation upon ligand-binding (54). With respect to type I IFN-induced signalling in human fibrosarcoma cells, kinase activity of TYK2 appears to be specifically required for IFNbeta-induced STAT3 and IFNAR1 but not for STAT1 and STAT2 phosphorylation (55). Accordingly, TYK2 kinase activity is redundant for the expression of some but not all interferon-stimulated genes (ISGs) in response to IFNbeta (56, 57). Furthermore, TYK2 has a dual role in the activation of STAT5 in response to type I IFN. TYK2 is required for STAT5 phosphorylation (58) but also activates the dual-specificity phosphatase VHR which then selectively dephosphorylates STAT5 (58, 59). Apart from the activation of STATs, IFNs activate a number of additional signalling cascades, some of which depend on TYK2 (60, 61). Moreover, TYK2 has been implicated in the IFN-induced activation of RNA-dependent protein kinase (PKR) (62).

4.2. IL-10 family

Interleukin (IL)-10 signals via IL-10R1 and IL-10R2, which associate with JAK1 and TYK2, respectively. The role of TYK2 in IL-10 signalling is not entirely clear and may be cell type- and/or context-dependent. In macrophages and $CD3^-$ splenocytes TYK2 is redundant for IL-10-induced STAT3 activation. IL-10-mediated suppression of TNF production in macrophages, up-regulation of MHC Class II in $CD3^-$ splenocytes as well as T cell proliferation in response to IL-2/IL-10 are unchanged in the absence of TYK2 (7, 8). Reduced IL-10-mediated STAT3 activation and reduced suppression of IFNgamma-induced nitrite production has been reported in a later study in *Tyk2*-deficient thioglycollate-elicited peritoneal macrophages (63). The TYK2-associated IL-10R2 chain is engaged by several additional members of the IL-10 family (i.e. IL-22, IL-26, IFNlambda1, IFNlambda2, and IFNlambda3) (64). These are more recently identified cytokines with only just emerging biological functions and often cell type-restricted expression of the second receptor chain. The role of TYK2 in the respective signalling cascades is still unknown. IFNlambda1, IFNlambda2 and IFNlambda3 (also known as IL-29, IL-28A and IL-28B) are functionally similar to type I IFNs and designated type III IFNs (65).

4.3. IL-12 family

TYK2 associates with IL-12Rbeta1, a receptor chain that is used by two members of the IL-12 family, i.e. the heterodimeric cytokines IL-12 and IL-23 that are composed of the p40 and p35 or p40 and p19 subunits, respectively (66). The second receptor chain for both cytokines (IL-12Rbeta2 and IL-23R, respectively) associates with JAK2. Although STAT1, STAT3, STAT4 and STAT5 can be activated by IL-12 and IL-23, biological responses are mainly mediated by STAT4 in response to IL-12 and STAT3 in response to IL-23. IL-12 signalling is clearly compromised in the absence of TYK2. STAT3 and STAT4 activation are strongly impaired and as a consequence *Tyk2*$^{-/-}$ activated splenocytes, T cells, natural killer (NK) cells and dendritic cells (DCs) fail to produce IFNgamma in response to IL-12 (7, 8, 67-70). In contrast, IL-12 costimulatory effects on T cell proliferation remain intact in the absence of TYK2 (8). TYK2 is also activated in response to IL-23 (71) and defective IL-23-induced STAT3 activation has been observed in T cell blasts derived from B10.Q/J mice (10). In line with these findings, IL-23-induced IFNgamma production in DCs (68) and IL-23-mediated IL-17 expression in gammadelta T cells and Th17 cells (72, 73) is impaired in the absence of TYK2.

4.4. IL-13 and IL-4

IL-13 can signal via the IL-4 receptor alpha (IL-4Ralpha) and the IL-13 receptor alpha1 (IL-13Ralpha1) chain and uses STAT6 as major signal transducer (74). TYK2 associates with IL-13Ralpha1 (75) and is required for the IL-13-induced 15-lipoxygenase activation in human monocytes (76, 77). IL-13Ralpha1/IL-4Ralpha is also utilized by IL-4 as an alternative receptor complex (74). The contribution of TYK2 to IL-4 responses remains to be determined.

4.5. IFNgamma and IL-18

TYK2 also indirectly impacts on signalling of IFNgamma and IL-18, even though these cytokines do not activate TYK2. IFNgamma signals through IFNGR1 and IFNGR2, which are associated with JAK1 and JAK2, respectively (47). Nevertheless, *Tyk2*-deficient fibroblasts and macrophages show reduced STAT1 activation in response to IFNgamma, which is most likely caused by a reduced STAT1 protein expression in the absence of TYK2 (7). Importantly, reduced levels of STAT1 protein in *Tyk2*-deficient cells might also impact on signalling and gene induction by other STAT1-utilizing cytokines. In addition, genes constitutively regulated by unphosphorylated STAT1 (78) might be similarly affected. The IL-18 receptor belongs to the IL-1 receptor superfamily and does not utilize JAKs for signal transduction (79). IL-18-mediated and IL-12/IL-18 synergistic induction of IFNgamma are reduced in TYK2-deficient NK and T cells (67). This is at least partly caused by reduced IL-18 receptor (IL-18R) expression and impaired IL-12-mediated upregulation of IL-18R in the absence of TYK2. It cannot be excluded that other effects, such as cross-talk between the different signalling cascades at either the receptor level or by additionally activated signalling cascades, contribute to this phenotype.

4.6. Other TYK2-activating cytokines

A number of cytokines induce TYK2 phosphorylation but do not require TYK2 for signal transduction. Prominent examples are cytokines sharing the gp130 receptor subunit (IL-6, leukaemia inhibitory factor (LIF), oncostatin M (OSM), ciliary neurotrophic factor (CNTF), cardiotrophin-1 (CT-1), IL-11, and IL-27) that

induce phosphorylation of JAK1, JAK2 and TYK2 (80). TYK2 is redundant for at least IL-6- and LIF-induced STAT3 activation (7, 8, 81). Similarly, TYK2 phosphorylation occurs in response to granulocyte colony-stimulating factor (G-CSF) (82, 83), but neither *TYK2* mutant human nor *Tyk2*-deficient murine cells show any defect in G-CSF responses (7, 82). Also, TYK2 is phosphorylated in response to thrombopoietin (TPO) (84, 85) and enhances TPO receptor surface expression (86), but is not essential for TPO-induced signal transduction (7, 87).

5. BIOLOGICAL FUNCTIONS OF TYK2 IN SPECIFIC CELL TYPES

5.1. B cells and megakaryocytes

Type I IFNs can inhibit cell growth and induce apoptosis in a complex and cell type-specific manner. TYK2 is essential for IFNbeta-induced apoptosis and for IFNalpha and limitin-induced growth inhibition of murine pro-B cells (88-90). Interestingly, these effects are STAT1-independent and require STAT3. Possibly causatively linked, mitochondrial respiration is reduced in pro-B cells in the absence of TYK2 both before and after IFNbeta treatment (91). TYK2 kinase activity is redundant in resting cells but needed to maintain mitochondrial respiration once cells are exposed to IFNbeta. It is currently unclear, how TYK2 influences mitochondrial function, however, in IFNbeta-treated cells this is at least partially mediated by STAT3. In addition, IFNalpha and limitin-mediated growth suppression of murine megakaryocytes also requires TYK2 but, in contrast to B lymphocytes, depends on the presence of STAT1 (92).

5.2. Mast cells

Cell type-specific TYK2 functions in type I IFN responses have been reported in murine mast cells as compared to fibroblasts. Mast cells show a stronger dependence on TYK2 for IFNalpha-induced STAT1 phosphorylation and target gene expression (93). Notably, lower levels of *Ifnar1* mRNA were reported in these cells and it might be interesting to determine whether receptor density impacts on TYK2 dependence. In addition, mast cells utilize specific and alternative receptor complexes for IL-15 signalling (94). Although IL-15-mediated phosphorylation of TYK2 has been reported (95), the exact role of TYK2 in IL-15 signalling is unclear.

5.3. Macrophages

A number of studies addressed the function of TYK2 in murine macrophage innate immune responses. Already the basal gene and protein expression patterns are influenced by the absence of TYK2 (96-98). At the transcriptome level, this mainly affects type I IFN-inducible genes (96). This is particularly important, since the impact of low-level constitutive type I IFN signalling on innate immune responses is becoming increasingly evident (99-102). Consistently, *Tyk2*-deficient macrophages show dramatically decreased intrinsic antiviral activity against Murine Cytomegalovirus (MCMV) (103). Autocrine/paracrine actions of type I IFN in response to lipopolysaccharide (LPS) and after MCMV infection are reduced in *Tyk2*$^{-/-}$ macrophages, especially at early time points (7, 98, 103). Absence of TYK2 likely also results in a reduced IFNalpha/beta production due to an impaired positive amplification loop (98). Moreover, TYK2 affects translational regulatory pathways (104), as *Tyk2* deficiency results in enhanced mRNA translation of specific genes (e.g. *IL-1beta*) after LPS treatment. The mechanism of TYK2-mediated translational suppression is unknown but likely occurs via IFNAR1- and STAT1-dependent mechanisms. This is of particular interest, since type I IFNs can on the one hand globally inhibit mRNA translation (62, 105-107) and on the other hand increase mRNA translation of certain ISGs (108).

5.4. Dendritic cells

In contrast to the TYK2-independent IL-12 production in LPS-treated macrophages (98), DCs require TYK2 to efficiently produce IL-12 and IL-23 in response to LPS or CpG oligodeoxynucleotide stimulation (68). This might be due to an autocrine IL-12 amplification loop acting in DCs (109). Consistent with defective IFNgamma and IL-12 production, *Tyk2*-deficient DCs fail to promote Th1 differentiation upon antigen stimulation in co-culture experiments and *in vivo* (68). Despite the impaired production of IL-23, IL-17 production is increased if *Tyk2*$^{-/-}$ DCs are co-cultured with $CD4^+$ T cells. This may be explained by the impaired IL-12-induced IFNgamma production in the absence of TYK2, since IFNgamma can suppress IL-17 production in T cells (110) and anti-IFNgamma antibodies abolish this effect (68).

5.5. Natural killer cells and T lymphocytes

NK cells have been reported to require TYK2 for the up-regulation of their lytic activity (67). Both, IL-12 and IL-18 triggered cytotoxicity was reduced in *Tyk2*$^{-/-}$ NK cells when tested against the NK target cell line YAC-1. In line with this, *ex vivo* derived and IL-2 expanded *Tyk2*$^{-/-}$ NK cells killed YAC-1 cells as well as lymphoma cells less efficiently (111).

An important role for TYK2 in $CD8^+$ T cell function has been identified in cytotoxic T lymphocyte (CTL) assays (112). *Tyk2*-deficient $CD8^+$ T cells (on OT-1 background) were described to be significantly less capable of killing antigen (OVA)-expressing target cells (EG7). This defect in antigen-specific target cell lysis was confirmed in *in vivo* CTL assays. Following immunization with a peptide ($OVA_{257-264}$) and adjuvant specific killing was significantly decreased in *Tyk2*$^{-/-}$ mice. This TYK2-dependent defect in CTLs was linked to defective type I IFN signalling since *Ifnar1*$^{-/-}$ mice mimicked this phenotype.

6. CONSEQUENCES OF *TYK2* DEFICIENCY IN MICE

6.1. Impact of *Tyk2* deficiency on infectious diseases

Among the cytokines that require TYK2 for signalling, IL-12 and IFNalpha/beta have well established crucial functions in innate and adaptive immune responses to infections. In line with this, *Tyk2*$^{-/-}$ mice are generally

Table 1. Consequences of *Tyk2* deficiency on the host defence against infections

Pathogen *(route)*	Phenotype	Effects	Genetic background	Ref.
LCMV *(i.v.)*	---	$CD8^+$ CTL ↓	mixed 129/Sv/J, C57BL/6	(7)
	---	Splenic B cell loss ↓	*ns*	(89)
VV *(i.v.)*	Viral load (spleen)↑	---	mixed 129/Sv/J, C57BL/6	(7)
MCMV* *(i.p.)*	Survival ↓ Viral load ↑	---	C57BL/6	(103)
VSV *(i.v.)*	Survival modestly or not affected	---	mixed 129/Sv/J, C57BL/6	(7)
Listeria monocytogenes (i.p.)	Survival ↓ Bacterial load (spleen, peritoneum) ↑	Systemic IFNgamma levels ↓ IL-10 (splenic DCs) ↑ $CD8^+$ CTL ↓	*ns*	(122)
	---	Ag-specific $CD8^+$ T cell contraction ↓	C57BL/6	(123)
Escherichia coli (i.p.)	Bacterial load (peritoneum) ↑	Neutrophil recruitment ↓ gammadelta T cell IL-17 production ↓	C57BL/6	(72)
Leishmania major (footpad)	Footpad thickness ↑ Tissue parasite burden ↑	IFNgamma production by NK cells and $CD8^+$ T cells ↓ NK cell cytotoxicity ↓	mixed 129/Sv/J, C57BL/6	(70)
Toxoplasma gondii (i.p.)	Survival ↓	Systemic IFNgamma levels ↓ (delayed, IL-12-dependent)	B10.Q/J (BALB/c)	(124)

* salivary gland- and tissue culture-derived MCMV, respectively; *i.v.*, intravenous infection; *i.p.*, intraperitoneal infection; *ns*, not specified.

more prone to infectious diseases (Table 1). The most prominent activity of IL-12 in the course of infections is the stimulation of IFNgamma production by NK and T cells (66). In addition, IFNgamma can also be induced by IFNalpha/beta (113, 114). In both cases, transcriptional activation of the *Ifngamma* gene depends on STAT4, whereby IL-18-derived signals can synergize. The role of IL-23 in infectious diseases is just emerging. Protective functions have for example been reported against viral and bacterial infections, whereas the role during fungal diseases appears to be largely deleterious (115-117).

Efficient host defence against many viruses requires both functional IFNalpha/beta and IL-12 signalling, although to different extents. *Tyk2*$^{-/-}$ mice fail to efficiently mount $CD8^+$ CTL responses after infection with Lymphocytic Choriomeningitis Virus (LCMV) (7). Consistent with the role of TYK2 in mediating pro-B cell apoptosis *in vitro*, *Tyk2*-deficient mice show reduced B cell loss in spleen and bone marrow after LCMV infection (89). *Tyk2*$^{-/-}$ mice are also compromised in their defence against Vaccinia Virus (VV) infection, as they show increased viral load in spleens after intravenous infection (7). *Tyk2*$^{-/-}$ mice are highly susceptible to lethal challenge with MCMV and show increased viral titers in the spleen, liver, lung and salivary gland after sublethal MCMV infection (103). A surprisingly modest, if any, effect of *Tyk2* deficiency on survival rates is observed after Vesicular Stomatitis Virus (VSV) infection (7), a virus that is mainly controlled by type I IFN-dependent mechanisms (118). It remained unclear whether the reduced IFNalpha/beta responses in the absence of TYK2 suffice to control viral infections *in vivo* or whether the lack of a clear effect is specific for the VSV infection model used. Further work using other viral infection models is required to address this issue.

With respect to bacterial infections, IL-12 is generally protective (66) whereas IFNalpha/beta can be either sensitizing or protective (119). In the context of *Listeria monocytogenes*, IFNalpha/beta is clearly deleterious for the host and mice lacking IFNAR1 are less susceptible to intraperitoneal *L. monocytogenes* infection (120, 121). Despite this fact, survival of *Tyk2*$^{-/-}$ mice upon *L. monocytogenes* infection is significantly reduced (122). $CD4^+$ and $CD8^+$ T cells fail to produce IFNgamma in the absence of TYK2 and DC-priming of $CD8^+$ T cells is impaired. TYK2 is also required for antigen-specific $CD8^+$ T cell contraction in a *L. monocytogenes* infection model (123). More recently, increased bacterial load and defective IL-17 production by gammadelta T cells in response to intraperitoneal *Escherichia coli* infection were reported in *Tyk2*$^{-/-}$ mice. IL-23 production is unimpaired but IL-17 expression is reduced and correlates with reduced neutrophil numbers in the peritoneal cavity (72).

Tyk2-deficient mice show increased sensitivity to infection with protozoan pathogens. *Tyk2*$^{-/-}$ mice develop more severe skin lesions after infection with *Leishmania major* (70). IFNgamma production of NK and $CD8^+$ T cells is strongly decreased early after infection and NK cells display impaired cytotoxicity. At later stages of infection, IFNgamma production is partially restored and TYK2 is not needed for the eventual control of the disease. A defective IFNgamma production of $CD4^+$ and $CD8^+$ T cells is also observed after *Toxoplasma gondii* infection in B10.Q/J mice. Again, IFNgamma production occurs only delayed and can be restored by administration of recombinant IL-18 (124).

Summarizing the data obtained so far, the predominant effect of TYK2 deficiency during infections is a delayed or impaired IFNgamma production and the consequences thereof (Figure 3). Besides that, defective IL-23-mediated IL-17 production of gammadelta T cells constitutes another important defect in *Tyk2*$^{-/-}$ mice which may have important consequences for the defence against various pathogens. It can be speculated that IL-23-mediated maintenance of Th17 cells may also be affected by the absence of TYK2. However, *in vivo* evidence remains to be provided. Moreover, the partial impairment of IFNalpha/beta responses is likely to contribute to the

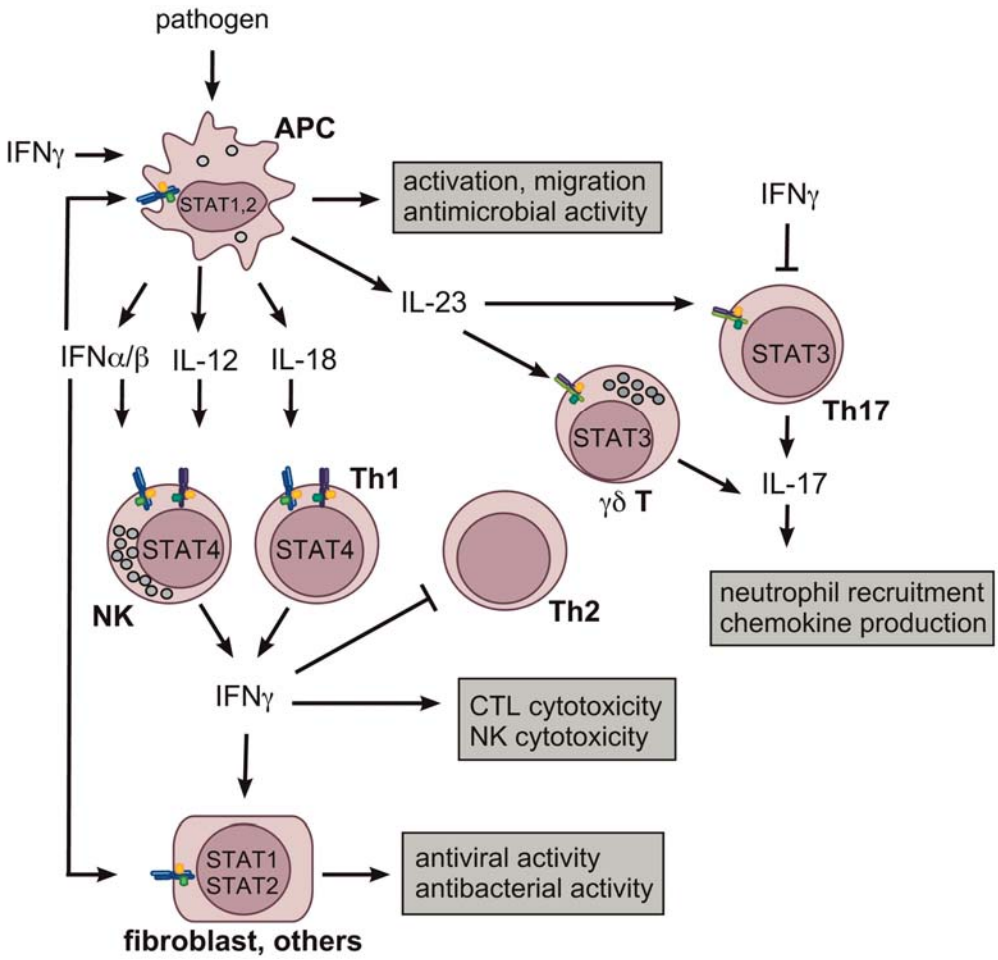

Figure 3. The role of TYK2 in immunity against infections. IFNalpha/beta, IL-12 and IL-18 are produced by antigen-presenting cells (APC, e.g. macrophages and DCs) upon pathogen encounter. IL-12 and IFNalpha/beta activate STAT4 in a TYK2-dependent manner in NK and Th1 cells. STAT4, alone or in combination with IL-18-derived signals, induces the expression of the *Ifngamma* gene. IFNgamma and IFNalpha/beta activate macrophages and DCs to e.g. induce more IL-12. IFNgamma and IFNalpha/beta also exert direct antiviral and antibacterial activity in most likely all cell types (e.g. fibroblasts) mainly via STAT1 or STAT1 and STAT2, respectively. IFNgamma promotes Th1 development and inhibits Th2 and Th17 differentiation. Furthermore, IFNgamma activates killing activity of NK and cytotoxic T cells (CTLs). IL-23 acts on gammadelta T and probably Th17 cells to induce IL-17 expression and this largely depends on the presence of TYK2 and STAT3.

increased sensitivity to viral infections. Again, the extent of this effect is unclear and needs further evaluation.

6.2. TYK2 in inflammation, allergy and autoimmune diseases

As opposed to infectious diseases, TYK2 mainly acts deleterious in inflammatory and autoimmune diseases (Table 2). Interestingly, this is not the case during contact hypersensitivity and future work is needed to understand the precise role of TYK2 in the underlying signalling networks. Again, the predominant effect of *Tyk2* deficiency seems to be an impaired IFNgamma production. Defective IL-23 responses likely also contribute but remain to be investigated in more detail.

Endotoxin shock is characterized by a severe systemic inflammatory response that frequently results in multi-organ dysfunction. *Tyk2*$^{-/-}$ mice survive high-dose LPS-induced endotoxin shock. IFNgamma and IFNbeta have substantial roles in the susceptibility to LPS, but only *Ifnbeta*$^{-/-}$ mice display comparable resistance to *Tyk2*$^{-/-}$ mice (98, 125, 126). *Tyk2*$^{-/-}$ mice show normal systemic levels of the pro-inflammatory cytokines TNF and IL-1beta, at least early after LPS challenge, but IFNgamma production is strongly impaired (98). However, it is clear that STAT1-independent mechanisms are involved since *Stat1*$^{-/-}$ mice succumb to a lower dose of LPS than *Tyk2*$^{-/-}$ mice (98, 125). Furthermore, *Tyk2*$^{-/-}$ mice show similar but less pronounced defects than *Ifnar1*$^{-/-}$ mice with respect to the induction of co-stimulatory molecules in splenocytes, but an organ-specific differential defect in inducible nitric oxide synthase expression (127, 128). It is currently unknown whether combinatorial effects of reduced IFNalphabeta signalling and IFNgamma production in

Table 2. Consequences of *Tyk2* deficiency on inflammation, allergy and autoimmune diseases

Disease model	Phenotype	Effects	Genetic background	Ref
LPS-induced shock	Survival ↑	Systemic IFNgamma levels ↓ Systemic IL-6, IL-1beta and TNF (early) ⇔	C57BL/6	(98)
	Survival ↑	Systemic IFNgamma levels ↓ Systemic TNF and IL-12p40 (↓)	mixed 129/Sv, C57BL/6	(125)
Intestinal I/R injury	Survival ↑	Tissue destruction (jejunum) ↓ Neutrophil recruitment (intestine) ↓ P-selection and ICAM expression (endothelium) ↓	C57BL/6	(129)
CHS	Ear swelling ↑	IFNgamma and IL-12 in skin tissue ↓ IL-2 and IL-4 in skin tissue ↑ STAT3 and STAT4 phosphorylation in draining LN cells (↓)	129/Ola	(146)
EAE	Clinical score ↓	IFNgamma and IL-6 production (*in vitro* re-stimulation) ↓	B10.Q/J (B10.D1-H2^{q}/SgJ)	(130)
	Clinical score ↓	Th1, Th17 cell, macrophage and neutrophil infiltration (spinal cord) ↓ Peripheral Th17 cell numbers ⇔ Th1 cell-mediated disease (adoptive transfer)	C57BL/6	(73)
Allergic lung inflammation	--	Th2 differentiation ↑ IgE production (serum) ↑ IL-4, IL-5, IL-13 (BALF) ↑ Eosinophil recruitment ↑ Goblet cell hyperplasia ↓	BALB/c	(144)
CIA	Disease score ↓	IFNgamma production in LN cells ↓ IgG1, IgG2a (serum) ↓	B10.Q/J (B10.D1-H2^{q}/SgJ)	(69)

I/R, ischemia/reperfusion; CHS, contact hypersensitivity; EAE, experimental autoimmune encephalomyelitis; CIA, collagen-induced arthritis; LN, lymph node; BALF, bronchioalveolar fluid.

Tyk2$^{-/-}$ mice are sufficient to confer the high LPS resistance. Notably, increased resistance of *Tyk2*$^{-/-}$ mice was also reported in an intestinal ischemia/reperfusion shock model (129).

Up to now, TYK2 has been reported to aggravate autoimmune diseases in two different murine disease models. The *Tyk2* mutant B10.Q/J mouse strain is resistant against collagen-induced arthritis (CIA). Lymph node cells from these mice fail to produce IFNgamma in response to antigen stimulation and the mice show reduced production of IgG2a and IgG1 collagen-specific antibodies (69). More recently, two independent studies demonstrated an involvement of TYK2 in the development of experimental autoimmune encephalomyelitis (EAE). B10.Q/J and *Tyk2*$^{-/-}$ mice show increased resistance against myelin oligodendrocyte glycoprotein (MOG)-induced EAE (73, 130). In *Tyk2*$^{-/-}$ mice reduced infiltration of macrophages, neutrophils, Th1 cells and Th17 cells in the spinal cord was reported. However, normal numbers of MOG-specific Th17 cells were found in draining lymph nodes (73). This is surprising, since *Tyk2*-deficient Th17 cells fail to respond to IL-23 *in vitro* (73) and *Il23*$^{-/-}$ and *Il23R*$^{-/-}$ mice have clearly reduced numbers of MOG-specific Th17 cells (131-133). Thus either TYK2 is dispensable for IL-23 responses *in vivo* or other TYK2-dependent mechanisms counteract the defects. Possibly, reduced levels of IFNgamma in the absence of TYK2 might facilitate the generation of Th17 cells, as IFNgamma inhibits Th17 differentiation (134, 135). Importantly, adoptive transfer experiments demonstrated that TYK2 in T cells is required for the development of EAE, whereas TYK2 in the cellular environment is dispensable, arguing for a crucial role of TYK2 in pathogenic CD4^{+} T cell responses (73). Surprisingly, reduced IL-6 production was found in B10.Q/J lymph node cells in *ex vivo* restimulation assays, however, the *in vivo* relevance of this finding remains to be determined (130). *Il6*$^{-/-}$ mice show increased resistance against EAE (136-139) and neutralization of IL-6 blocks the development of EAE and the generation of myelin-specific Th17 cells (140). *Ifngamma*- and *Ifngr1*-deficient mice display increased sensitivity to EAE (141, 142), but IFNgamma can also act disease promoting (143). In line with the resistance of *Tyk2*$^{-/-}$ and B10.Q/J mice to EAE, quantitative trait locus (QTL) analyses demonstrated a correlation of TYK2 inactivity with increased central nervous system (CNS) repair in a Theiler's virus infection model (11).

Although TYK2 is not directly involved in the generation of Th2 cells, Th2 differentiation can be inhibited by TYK2-dependent Th1 cell-derived signals. Accordingly, *Tyk2*$^{-/-}$ mice show increased Th2 development and are highly susceptible to Th2 cell-mediated allergic airway inflammation (144). *Tyk2*$^{-/-}$ mice show increased antigen-specific IgE production and increased eosinophil and CD4^{+} T cell recruitment in the airways. In contrast, the number of goblet cells and the expression of a mucin gene after antigen-inhalation were reduced in *Tyk2*$^{-/-}$ mice. Since IL-13 is crucial for epithelial goblet cell hyperplasia and mucin gene expression (145), these results support *in vitro* data arguing for an essential role of TYK2 in IL-13 signalling.

Surprisingly, *Tyk2*$^{-/-}$ mice are highly susceptible to hapten-induced contact hypersensitivity (CHS), a disease that is believed to be promoted by IL-12/IFNgamma. Ear swelling during CHS is increased, whereas levels of IFNgamma and IL-12 at the reaction site are lower and levels of IL-2 and IL-4 higher in the absence of TYK2 (146). Studies with a large number of different knockout mice revealed crucial, sometimes opposing roles of TYK2-activating cytokines in the development of CHS (147) and it will be of interest to determine how TYK2 balances immune responses towards CHS resistance.

6.3. TYK2 and cancer

Thus far, only a few studies addressed the role of TYK2 for tumour development and surveillance (Table 3). The first link of TYK2 to cancer formation has been observed in studies on murine lymphoid malignancies (111). Animals deficient for TYK2 develop Abelson murine leukaemia virus-induced B lymphoid leukaemia/lymphoma as well as Tel-JAK2-induced T lymphoid leukaemia with a higher incidence and shortened latency. The high susceptibility of *Tyk2*$^{-/-}$ mice to lymphoid tumours was the result of an impaired tumour surveillance rather than a tumour cell intrinsic effect. In particular, *Tyk2*-deficient NK and NKT cells showed decreased cytotoxic capacity. Later reports verified a role of TYK2 also for T cell-mediated tumour surveillance and showed that *Tyk2*$^{-/-}$ mice are highly tumour-prone when challenged with tumour cells that are under the control of CTLs such as EL4 cells (112). Although TYK2 was described to be dispensable for the maturation of DCs, *in vitro* and *in vivo* assays revealed a severe impairment of $CD8^+$ T cell-mediated cytotoxicity upon *Tyk2* deficiency. This reduced CTL-dependent killing could be linked to an impaired type I IFN signalling, since tumours derived from an OVA-expressing derivative of the EL4 cell line (EG7) grew faster in *Tyk2*$^{-/-}$ and *Ifnar1*$^{-/-}$, but not in *Ifngamma*$^{-/-}$ or *Il12p35*$^{-/-}$ mice. Further support for this concept comes from a vaccination study using neutralizing antibodies against type I IFN where the importance of type I IFN for the generation of tumour specific CTLs has been determined (148). In contrast to the essential role of TYK2 in tumour surveillance, TYK2 seems to be of less importance for transformation or tumour cell intrinsic effects. The absence of TYK2 neither affects Abelson murine leukaemia virus-induced transformation (111), nor latency in an FLT3-ITD (FLT3 tyrosine kinase-internal tandem duplication) bone marrow transplantation model that leads to lethal myeloproliferative disease/acute myeloid leukaemia (AML) (149). However, TYK2 has been implicated in metastasis and tumour cell infiltration in human patients (150). A similar observation has been made in Emu-Myc transgenic mice, where the lack of TYK2 significantly reduced tumour cell infiltration into the liver, however, the formation of solid B cell lymphomas occurred irrespective of the presence of TYK2 (151). Although the JAK/STAT signalling cascade has been implicated in chemokine signalling, which may be involved in tissue infiltration (152-154), the mechanism of how exactly TYK2 could influence tumour cell invasiveness still needs to be addressed.

7. TYK2 IN HUMAN DISEASES

Up until now, only one patient with TYK2 deficiency has been reported (155). This patient presented with a clinical phenotype overlapping with that of autosomal recessive hyper IgE syndrome, suffered from atopic dermatitis and had recurrently suffered from infectious diseases, including dermal Herpes Simplex Virus infections, oral candidiasis, salmonella gastroenteritis and Bacille Calmette-Guerin (BCG) infection. The *TYK2* gene of this patient displayed a homozygous deletion (nt 550-553) causing a frame-shift mutation from the amino acid position 70 (aa70) onwards resulting in a premature stop codon at aa90. No TYK2 protein could be detected in cells derived from this patient and the theoretical truncated protein consists only of parts of the FERM domain. T cells and peripheral blood mononuclear cells (PBMCs) from this patient are completely unresponsive to both IFNbeta and IFNalpha with respect to phosphorylation of STATs1-4 and the induction of IFN target genes, respectively. Neither IFNalpha nor IFNbeta could establish an antiviral state against Herpes Simplex Virus infection in the patient's B cells. Consistent with TYK2 mutant human cell lines, the patient's T cells show reduced IFNAR1 surface expression. Interestingly and as reported for murine cells derived from *Tyk2*-deficient mice, basal STAT1 protein levels and IFNgamma-mediated gene induction are reduced in patient's cells. Furthermore, the patient's T cells show no detectable STAT4 phosphorylation and reduced IFNgamma secretion in response to IL-23. PBMCs derived from the patient have a reduced induction of SOCS3 by IL-10 and macrophages show reduced inhibition of LPS-induced TNF production by IL-10. In contrast to the redundant role of TYK2 for IL-6-induced STAT3 activation in both human and murine cells, the patient's T cells do not induce SOCS3 in response to IL-6. Consistent with observations in *Tyk2*-deficient mice, the patient's T cells exhibit a reduced Th1 and accelerated Th2 differentiation *in vitro* (155).

Over the last years several reports on TYK2 and human cancer have emerged. Overexpression of *TYK2* has been found in human breast cancer cell lines (156) and in human tumours, such as prostate cancer and squamous cervical carcinoma (150, 157). In these tissues TYK2 protein levels seem to be specifically elevated in malignant cells compared to the non-transformed surrounding healthy tissue. Importantly, inhibition of TYK2-dependent signalling by siRNA or by employing a TYK2 inhibitor significantly reduced the invasiveness of prostate cancer cells *in vitro* (150). More recently it was reported that blocking TYK2 activity also inhibits the migration of a cell line originating from breast cancer (158). These data suggest that TYK2 has an important role in facilitating the invasion of malignant cells and that TYK2 inhibition might be a useful strategy to prevent metastatic tissue infiltration. Support for this notion has been obtained in a murine model (see above).

Besides sporadic somatic mutations that accumulate in the developing tumour due to cancer genome instability, a *TYK2* single nucleotide polymorphism (SNP) has been associated with tumour formation (159). The polymorphism leads to a pointmutation in the kinase domain of TYK2 (P1104A) and was found in four independent tumour tissues (1 out of 37 breast tumours, 2 out of 9 colon tumours and 1 out of 10 stomach tumours). The TYK2 P1104A variant was also detected in about 7% of AML patient samples using high-throughput re-sequencing of the kinase domains of 26 tyrosine kinases in tumour samples of AML patients (160). Interestingly, expression of the TYK2 P1104A mutant in the *TYK2*-deficient human cell line U1A demonstrated decreased type I IFN-mediated phosphorylation and presumably decreased

Table 3. Consequences of *Tyk2* deficiency on tumour development

Tumour model	Phenotype	Effects	Genetic background	Ref.
Abelson-induced B cell leukaemia/ lymphoma	Survival ↓	NK-cell mediated tumour surveillance ↓	C57BL/6	(111)
Tel-JAK2-induced T lymphoid leukaemia	Survival ↓	---	C57BL/6	(111)
Transplantation of EL4/EG7 thymoma cells	Survival ↓ s.c. tumours ↑	CTL-mediated tumour surveillance ↓	C57BL/6	(112)
Emu-Myc-induced B cell lymphoma	---	Tumour cell infiltration into liver ↓	C57BL/6	(151)

s.c., subcutanous injection

kinase activity of TYK2 P1104A. P1104 is one of the first anchoring residues in the helical region of the kinase domain (29). In JAK2 deletion and mutation of structurally important residues in this region have been recently shown to abrogate kinase activity (161). Besides this germline mutation also 10 other non-synonymous sequence variants of *TYK2*, which are scattered over the whole *TYK2* gene, could be identified in this particular approach. By cDNA-based sequence analysis of the entire tyrosine kinase transcriptome of 254 tumour cell lines additional germline but also some somatic mutations of *TYK2* could be identified (162). Interestingly, a potential tumour-promoting effect of a *TYK2* polymorphism (TYK2 V362F) in brain, haematopoietic and lymphoid system was delineated. In contrast to the most prominent somatic mutation of a Janus kinase (JAK2 V617F), that is frequently associated with myeloproliferative disorders, the homologous mutation of TYK2 (V678F) has not yet been identified in human cancer (19, 163).

Genome-wide association studies in humans furthermore implicated the *TYK2* gene locus in a number of other human diseases. *TYK2* polymorphisms are associated with an increased risk of systemic lupus erythematosus (164-168) and the *TYK2* gene has been identified as susceptibility locus for multiple sclerosis (169-172), Crohn's disease (173, 174), psoriasis (175), and type I diabetes (176). Very recently, the relationship of *TYK2* gene polymorphisms and autoimmune/inflammatory diseases has been evaluated using a meta-analysis including 11 individual studies (177). Although these reports are meaningful in regard of our current knowledge about TYK2, these polymorphisms/mutations require further experimental evaluation to finally determine their relevance in disease development and/or progression.

8. OPEN QUESTIONS AND FUTURE PERSPECTIVES

TYK2 has emerged as crucial molecule in cytokine signalling and host immunity. Although thus far TYK2 is predominantly associated with IFNalpha/beta, IL-12 and more recently IL-23 signalling, several other less well-characterized cytokines can be predicted to rely at least partially on TYK2 for signal transduction. Future work will show whether these cytokines (e.g. IL-22, type III IFNs) indeed require TYK2 and how this impacts on immune responses. Another recurrent issue is the cell type specificity of signalling networks. Expression levels of *TYK2* and other signalling components are significantly different among cell types and can affect cellular responses. This is of particular importance *in situ*ations that require complex integration of multiple or potentially opposing signals. Several lines of evidence exist for kinase-independent functions of JAKs, including TYK2. Consequences of TYK2 kinase-inhibition as opposed to the complete loss of TYK2 protein will require future attention, in particular when considering TYK2 kinase inhibition as target for therapeutic intervention. TYK2-specific inhibitors are currently being developed (29, 178, 179) and might be a useful strategy for the treatment of inflammatory and autoimmune diseases and to prevent tumour cell invasiveness. The very recent and surprising report that JAK2 mediates histone phosphorylation (180) raises the attractive possibility that also other JAK family members exert so far unrecognized biological functions. Finally, further characterization of *TYK2* naturally-occuring variants and immunological consequences in human patients is another important future challenge.

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Abbreviations: AML: acute myeloid leukemia, CHS: contact hypersensitivity, CIA: collagen-induced arthritis, CNTF: ciliary neurotrophic factor, CT-1: cardiotrophin-1, CTL: cytotoxic T lymphocyte, DC: dendritic cell, EAE: experimental autoimmune encephalomyelitis, FERM: four-point-one, ezrin, radixin, moesin, G-CSF: granulocyte colony-stimulating factor, IFN: interferon, IFNAR1: IFNalpha/beta receptor 1, IFNGR1: IFNgamma receptor 1, IL: interleukin, ISG: IFN-stimulated gene, JAK: Janus kinase, LCMV: Lymphocytic Choriomeningitis Virus, LIF: leukemia inhibitory factor, LPS: lipopolysaccharide, MCMV: Murine Cytomegalovirus, MOG: myelin oligodendrocyte glycoprotein, NK cells: natural killer cells, OSM: oncostatin M, PTPB: phosphotyrosine phosphatase B, SH2: src-homolgy 2, SOCS: suppressor of cytokine signalling, STAT: signal transducer and activator of transcription, TPO: thrombopoietin, TNF: tumour necrosis factor, TYK2: tyrosine kinase 2, VSV: Vesicular Stomatitis Virus, VV: Vaccinia Virus

Key Words: Janus kinase, TYK2, Signalling, Immunity, Infection, Cancer, Review

Send correspondence to: Birgit Strobl, Institute of Animal Breeding and Genetics, University of Veterinary Medicine Vienna, Veterinaerplatz 1, A-1210 Vienna, Austria, Tel: 0043 1 25077-5604, Fax: 0043 1 25077-5693, E-mail: birgit.strobl@vetmeduni.ac.at