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Tyrosine kinase 2 – Surveillant of tumours and bona fide oncogene

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ABSTRACT

Tyrosine kinase 2 (TYK2) is a member of the Janus kinase (JAK) family, which transduces cytokine and growth factor signalling. Analysis of TYK2 loss-of-function revealed its important role in immunity to infection, (auto-) immunity and (auto-) inflammation. TYK2-deficient patients unravelled high similarity between mice and men with respect to cellular signalling functions and basic immunology. Genome-wide association studies link TYK2 to several autoimmune and inflammatory diseases as well as carcinogenesis. Due to its cytokine signalling functions TYK2 was found to be essential in tumour surveillance. Lately TYK2 activating mutants and fusion proteins were detected in patients diagnosed with leukaemic diseases suggesting that TYK2 is a potent oncogene. Here we review the cell intrinsic and extrinsic functions of TYK2 in the characteristics preventing and enabling carcinogenesis. In addition we describe an unexpected function of kinase-inactive TYK2 in tumour rejection.

1. Introduction

The non-receptor tyrosine kinase 2 (TYK2) is a member of the Janus kinase (JAK) family consisting of three additional members (JAK1-3). Cytokine binding to and activation of the respective receptor complexes activate JAKs by auto- or trans-phosphorylation. Subsequently JAKs phosphorylate intracellular receptor chain residues and activate a family of transcription factors termed signal transducers and activators of transcription (STATs, comprised of STAT1-4, STAT5A, STAT5B and STAT6). Phosphorylated STATs re-orientate in their homo- or heterodimeric conformation and translocate into the nucleus to induce specific gene transcription. The resulting gene expression program drives various cellular mechanisms like proliferation, differentiation or death [1,2]. TYK2 was the first JAK family member genetically linked to cytokine, i.e. interferon (IFN) responses [3]. Further analyses of mutant human cells unresponsive to cytokines revealed that all JAKs are major players in signal transduction of cytokines [4–7]. Today it is well established that defined combinations of mono- or multimeric cytokine receptor complexes associated with JAKs and STATs drive the response to cytokines and growth factors [8,9].

The JAK–STAT pathway is evolutionary highly conserved [10]. The most ancient TYK2 orthologs have been identified in fish [11,12]. Gene targeted mice determined the *in vivo* loss-of-function (LOF) phenotypes for the *Jak* loci. In contrast to the lethality of lack of JAK1 and JAK2 [13–15] and the severe combined immunodeficiency of lack of JAK3 [16,17], TYK2 LOF does not lead to pathology under conventional housing conditions. Only upon immunological challenges $Tyk2^{-/-}$ mice show pathological phenotypes. *Tyk2*-deficient mice have been reported by three different groups [18–20]. Additionally, a naturally occurring TYK2 mutant B10.D1-$H2^{q}$/SgJ mouse strain has been discovered [21]. Recently further naturally occurring mutations in SJL/J and SWR/J mouse strains resulting in reduced TYK2 expression have been identified [22]. A floxed mouse model ($Tyk2^{fl/fl}$) allows cell type-specific deletion of TYK2 [23]. It becomes increasingly evident that JAKs display functions, which are independent of their enzymatic activity and/or receptor association. Both mouse and human TYK2 have been shown to exert these non-canonical functions [24–27]. The generation of a kinase-inactive TYK2 mouse ($Tyk2^{K923E}$) enables the investigation of non-canonical TYK2 *in vivo* [28]. The data from TYK2 LOF and mutant patients increase constantly and underscore the validity of the murine models for the translation into human pathophysiology and clinical settings [29–32].

The biological role of TYK2 has been mainly established in the context of host responses to infectious agents and of (auto-) immune or (auto-)inflammatory diseases [25]. The importance of TYK2 in tumour immunosurveillance has been also established [33]. While the role for other JAKs as drivers in the development of cancer has been intensively studied since many years, the significance of cell intrinsic TYK2 in oncogenesis has been revealed only recently [34,35].

In this review we will shortly recapitulate the structural features of TYK2 and its established functions in immunity and

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inflammation. We will focus on novel reports regarding TYK2's involvement in tumour surveillance and carcinogenesis.

2. TYK2 structure, stability and post-translational modifications

TYK2 has been identified more than 25 years ago [36,37]. It is located on chromosome 19 in humans and chromosome 9 in mice. TYK2, as the other JAKs, is a relatively large protein with a molecular weight of ~130 kDa. The sequence homology organizes JAKs into seven JAK homology (JH) domains 1–7 [38]. Structurally JAKs consist of four different domains: the N-terminal 4.1, Ezrin, Radixin, Moesin (FERM) domain, the Src homology 2 (SH2) domain, the pseudokinase domain and the C-terminal kinase domain [38,39] (see Fig. 1). The FERM domain (JH7-5 and a part of JH4) mediates stable association of JAKs with receptor domains. So far only shown for JAK2 and JAK3 it is also involved in kinase activity regulation [40,41]. The SH2 domain (half of JH4 and JH3) is involved in receptor binding [42]. The pseudokinase domain (JH2) has a canonical kinase domain that lacks catalytical function despite binding ATP [43] and is important for regulating the activity of the kinase domain [39,44]. Interestingly, the JAK pseudokinase domain is frequently mutated in human cancer patients [39,44]. The C-terminal kinase domain (JH1) harbours the catalytically active kinase with the two conserved tyrosine residues in the activation loop (see below). So far the molecular mechanism how the JAK pseudokinase regulates the activity of the kinase domain is not fully understood. A recent crystal structure of the kinase/pseudokinase domains of TYK2 indicates that the pseudokinase domain exerts an autoinhibitory function on the kinase domain, which becomes activated upon receptor dimerization [45,46]. Activation of TYK2 occurs by phosphorylation at Y1054/Y1055 in humans and Y1047/Y1048 in mice [25] (see Fig. 1). Several other

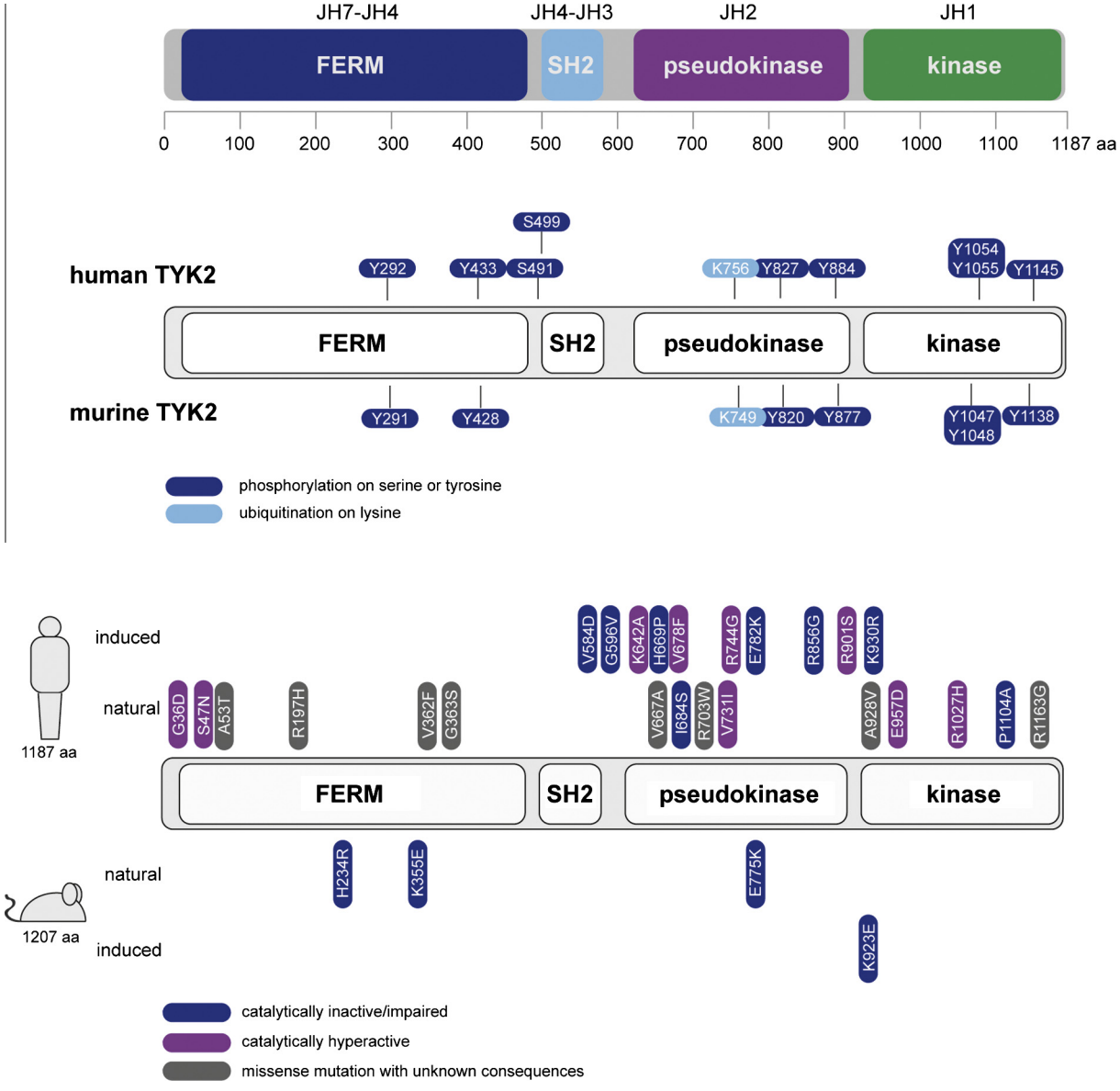

Fig. 1. Schematic TYK2 structure, post-translational modification and mutation sites of TYK2 in mice and men. Upper panel. TYK2 consists of four structural domains ranging from JAK homology (JH) domain 1–7 indicated on top. The amino acid scale of human TYK2 is depicted; murine TYK2 is 1180 aa (www.uniprot.org) in length. Middle panel. Phosphorylation (dark blue) and ubiquitination (light blue) sites in human TYK2 (top) and orthologous residues in murine TYK2 (below) are indicated. Lower panel. Naturally occurring and induced amino acid variants along TYK2 are depicted for humans (top, see Refs. [46,99,106,191,193,199–202]) and mice (bottom, see Refs. [21,22,28]). Mutations resulting in catalytically inactive or impaired TYK2 variants are depicted in blue, catalytically hyperactive TYK2 variants are shown in pink. Missense mutations with so far unknown consequences are illustrated in grey.

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