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Biochemistry and biology of the inducible multifunctional transcription factor TFII-I: 10 Years Later

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Abstract

Exactly twenty years ago TFII-I was discovered as a biochemical entity that was able to bind to and function via a core promoter element called the Initiator (Inr). Since then several different properties of this signal-induced multifunctional factor were discovered. Here I update these ever expanding functions of TFII-I--focusing primarily on the last ten years since the first review appeared in this journal.

Introduction

The temporal and spatial regulation of gene expression determines fundamental biological outcomes including lineage differentiation, cellular proliferation, survival and death. One major mechanism for bringing about such changes is at the level of transcription. Normal cells proliferate and acquire effector functions in a tightly regulated fashion in response to extrinsic signals that are transduced through specific cell surface receptors to the nucleus to control gene expression (Jones, 2007). Consequently, a breakdown in transcriptional regulatory pathways results in abnormal cellular functions causing various malignancies, immune deficiencies and other human disorders.

An important way of accomplishing signal transduction is via inducible transcription factors that reside latently in the cytoplasm but translocate to the nucleus upon signaling (Brivanlou and Darnell, 2002). Examples of these include NF- κ B, STAT and NFAT factors. Although these factors are tethered to the cytoplasm, thereby prevented from nuclear translocation in the absence of signals, they exclusively have nuclear functions. In contrast, a small group of factors, originally thought to have either exclusive cytoplasmic function or nuclear function, are now shown to have both functions. These include voltage-gated calcium channels (VGCC) or the derived fragment called calcium channel-associated transcriptional regulator (CCAT), DREAM and TFII-I (Naranjo and Mellstrom, 2007; Roy, 2007). Interestingly, in all three cases, the transcriptional activity appears to be regulated at least in part by signaling

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via calcium channels. While, the first two factors do not seem to be directly regulated by phosphorylation, TFII-I activity associated with both its cytoplasmic as well as nuclear residency requires phosphorylation (Roy, 2007).

TFII-I was discovered as a biochemical entity capable of binding to and functioning via the Initiator element (Inr) in *in vitro* reconstituted system with partially purified general transcription factors (Roy et al., 1991). Apart from its interaction with the Inr element, TFII-I also interacted with an upstream E-box element that is generally recognized by helix-loop-helix (HLH) proteins like USF. Interaction of TFII-I with an E-box was observed individually as well as cooperatively with USF (Roy et al., 1991, Roy et al., 1997). While binding and function of TFII-I via the Inr element has been noted since then in several instances both *in vitro* and *in vivo* (Roy, 2007), it does not appear to be a general transcription factor required for all Inr-containing promoters, particularly when assayed in *in vitro* transcription systems with highly purified transcription factors. Whether there are functionally distinct classes of Inr elements and corresponding factors (TFII-I being one of them) or whether interaction of TFII-I with the Inr element is required for steps beyond transcription initiation remains currently unresolved. Instead, the role of TFII-I in mediating signal-dependent transcription in various biological contexts has gained more prominence over the last 10 years and this review will predominantly focus on these properties of TFII-I.

Structural properties of TFII-I

TFII-I (the gene symbol is *GTF2I* in humans and *Gtf2i* in mice) belongs to a family of transcription factors, consisting of three related genes that are closely located in human chromosome 7, a portion of which is deleted in a haplo-insufficient manner in Williams-Beuren syndrome (WBS) (Hinsley et al., 2004). Each family member has multiple alternatively spliced isoforms. The best characterized is TFII-I, which has at least four alternatively spliced isoforms in humans (α , β , γ and Δ) (Roy, 2001). A special structural characteristic of TFII-I family members is the presence of a repeated domain (Roy, 2001). For instance, TFII-I has six such repeats (Fig 1a), each containing a putative HLH motif that is a protein-protein interaction module traditionally present in E-box binding proteins. The most conserved amino acids within these repeats are called the I-repeats (Fig 1b) (Roy et al., 1997). However, there are differences between TFII-I HLH motifs and traditional HLH motifs noted both by structure prediction and actual determination of solution structure of one of the TFII-I repeats. For instance, NMR spectroscopic determination of the three-dimensional structure of the fifth repeat in TFII-I revealed that the TFII-I/GTF2I domain consists of four helices, two anti-parallel strands/sheets (between helices 2 and 3 and between helices 3 and 4) and a long loop comprising of two β -turns between helices 2 and 3 (Fig 1c) (Doi-Katyama et al., 2007). It is likely that all other repeats of TFII-I have similar folds (henceforth called the “I-fold”) because the conserved residues commonly present in the various repeats are assembled on the hydrophobic core, β -turns and other secondary structural elements (Doi-Katyama et al., 2007). PSI-PRED structure prediction also proposes similar folds in TFII-I (Hinsley et al., 2004). Thus, although TFII-I functionally behaves as an HLH protein in certain ways (for instance, binding to an E-box and interacting with USF), structurally it is not a classical HLH protein and appears to have a unique structural fold not present in any other known proteins. TFII-I might utilize these repeats not only for intermolecular homo- or heteromerization, but also for intramolecular interactions between various repeats thereby producing “conformational isomers”.

Apart from the I-fold, all members of the TFII-I family exhibit a conserved N-terminal leucine zipper (LZ) domain, which is usually involved in dimerization (Fig 2). Although the precise function of the LZ in TFII-I family members is not known, a truncated mutant of TFII-I lacking the N-terminal 90 amino acids including the LZ, fails to bind DNA (Roy,

2001). This failure does not appear to involve dimerization as the mutant forms dimers. Interestingly, the N90 mutant does not interact with the native Δ -isoform but interacts readily with the β -isoform. These observations, along with other supporting biochemical evidence, suggest that the LZ is buried in the Δ -isoform, which assumes a constitutive “closed” conformation and which undergoes signal-induced “opening” to form stable dimers. In contrast, the β -isoform is constitutively open and readily forms dimers. Because the Δ -isoform undergoes signal-induced nuclear translocation, while the β -isoform resides constitutively in the nucleus, it is conjectured that dimerization is necessary for nuclear translocation. According to this model, while the I-fold domain initiates dimerization, LZ stabilizes such dimeric interactions that could be regulated by extracellular signaling (Roy, 2001). A recent study further confirms the essential role of the N-terminal region in TFII-I. Homozygous or heterozygous mutant mice, lacking the N-terminal 140 amino acids exhibit significant craniofacial abnormalities. While the heterozygous mice also exhibit abnormal neurobehavioral characteristics, the homozygous mice present compromised embryonic viability and fertility (Lucena et al., 2010).

Given that TFII-I binds to both Inr/Inr-like elements as well as E-box elements (Roy et al., 1997), it is also of considerable interest to elucidate its DNA binding domains. Preceding helix 1 in repeat 2, there is a stretch of basic residues (amino acids 301–306), which function as a DNA binding domain since deletion of these residues abrogated binding to Inr/Inr-like elements at the V β and *c-fos* promoters (Roy 2001). It is currently not known whether the same residues also contribute to the E-box binding. TFII-I family member Ben (also called MustRD1, GTF2IRD1, GTF3) contains 5 repeats (Fig 2) and exhibit interesting binding pattern (Hinsley et al., 2004). While isolated repeats 2, 4 and 5 bound similar sequences in SELEX site selection assays, repeat 3 exhibited more relaxed sequence requirements and repeat 1 did not bind DNA at all. In the same study, individual repeats 4 and 6 of TFII-I were also subjected to site selection, although these isolated repeats showed very modest DNA binding activity (Vullhorst and Buonanno, 2005). Added to these difficulties is the fact that the stoichiometry of DNA bound TFII-I (and other family members) is currently unknown. These results suggest that different TFII-I family members might utilize different DNA binding mechanisms and that each member might have more than one DNA binding domain. In summary, the TFII-I family proteins do not appear to follow classical protein-protein and/or protein-DNA interaction patterns (Anantharaman et al., 2011). Further biochemical and structural studies are necessary to elucidate these patterns.

An interesting aspect of TFII-I family members recently came to light. Database search predicted short/truncated alternatively spliced isoforms for all members (Hinsley et al., 2004). These isoforms contain the LZ and at least the first repeat but they do not exhibit either the basic region/DNA binding domain or any recognizable nuclear localization signal (NLS). Therefore, it is tempting to conjecture that these short isoforms naturally behave as dominant negatives to curtail functions of the wild type proteins. Moreover, the shortest family member (GTF2IRD2) has only the LZ and the first two repeats without the BR or NLS (Fig 2) (Hinsley et al., 2004; Makeyev et al., 2004). Although this protein is largely uncharacterized at present, preliminary results suggest that GTF2IRD2 can interact with TFII-I and inhibit both nuclear localization and transcriptional functions of TFII-I (Antonell, A., Tussie-Luna, MI, Roy, AL and Perez-Juado, L., In preparation). How these interactions are regulated upon signaling and how these truncated proteins interact with the full-length family members are currently unknown.

Signal-Induced Transcriptional functions of TFII-I

Since the discovery that TFII-I is phosphorylated at multiple residues and in response to various signaling pathways (Cheriyath et al., 2002; Novina et al., 1998), there have been a number of studies placing TFII-I in signal-induced transcriptional regulation under different

biological contexts. Although TFII-I has also been reported to be SUMOylated (Zhao et al., 2004) and interacts with PIASx- β , a SUMO E3 ligase (Tussie-Luna et al., 2002), the functional significance of this modification is yet to be fully appreciated.

Growth factor signaling

TFII-I was shown to be required for mitogen induced transcriptional activation of the *c-fos* gene by binding to several sites on the promoter together with SRF and STAT1/STAT3 (Grueneberg et al., 1997; Kim et al., 1998). Both growth factors (e.g., epidermal growth factor, EGF; platelet derived growth factor, PDGF) and serum trigger phosphorylation of TFII-I. The tyrosine 248 (Y248) is critical for signal-induced transcriptional activity of TFII-I and signal-induced nuclear TFII-I is phosphorylated at Y248, suggesting that this modification plays a role in nuclear translocation of TFII-I as well (Cheriyath et al., 2002; Roy, 2007). Y248 phosphorylated TFII-I also physically interacts with extracellular signal regulated kinase (ERK)-1/2 belonging to the mitogen activated protein kinase (MAPK) family (Roy, 2007). Given that ERKs do not have an intrinsic nuclear localization signal but translocate to the nucleus upon signaling, it was postulated that they are transported to the nucleus via direct interactions with TFII-I in response to signaling. Indeed, either deletion of the TFII-I NLS or silencing TFII-I by RNAi results in cytoplasmic accumulation of ERKs even in response to signaling (Hakre et al., 2006). As expected, *c-fos* transcriptional activation is significantly hampered under these conditions. Importantly, reconstitution with wild type TFII-I rescues both the ERK nuclear localization as well as *c-fos* transcriptional activation. That TFII-I does not merely carry ERKs across the nuclear membrane is demonstrated by the fact that a DNA binding deficient (Δ BR) mutant TFII-I that interacts with ERK1/2 and exhibits nuclear residency fails to activate *c-fos* transcription (Hakre et al., 2006).

Apart from the Ras/Erk signaling pathway, *c-fos* gene is also regulated by the Rho signaling pathway. The FF-domain-containing p190 Rho GTPase activating proteins (GAPs) are potent regulators of the Rho signaling pathways that respond to adhesion receptors and growth factors and mediate cytoskeletal changes. TFII-I was shown to specifically and directly interact with p190RhoGAP both *in vitro* and *in vivo* (Jiang et al., 2005). Importantly, p190 sequesters TFII-I in the cytoplasm via its FF domains, but upon PDGF receptor mediated phosphorylation of an FF domain, TFII-I is released from p190 and translocates to the nucleus to activate *c-fos*. These observations provide a rationale for how TFII-I might be tethered to the cytoplasm in resting state (Jiang et al., 2005). Moreover, they also suggest that TFII-I could link the Ras/ERK and Rho pathways to regulate *c-fos* and perhaps other mitogen responsive genes.

Although TFII-I has several alternatively spliced transcripts, roles of these isoforms were unknown. Using murine NIH3T3 fibroblasts, which appear to have only the Δ - and the β -isoforms, the signal-induced function of these isoforms were addressed. While the β -isoform was constitutively found in the nucleus, the Δ -isoform was predominantly cytoplasmic. Remarkably, upon signaling the β -isoform became cytoplasmic and the Δ -isoform was found in the nucleus (Hakre et al., 2006). Consistent with this subcellular switching, the β -isoform was recruited to the *c-fos* promoter in the basal state and the Δ -isoform was recruited to the same site only upon signaling (Fig 3). Equally important is the observation that silencing of the β -isoform results in activation of *c-fos*, while silencing of Δ leads to its repression (Hakre et al., 2006). In line with its presumptive repressive role, the β -isoform, in comparison to the Δ -isoform, appears to interact better with both co-repressors HDAC3 and LSD1 (I Tussie-Luna and A.L.R, unpublished). Thus, in the context of growth factor/mitogenic signaling, the two isoforms of TFII-I set a signaling switch to transcriptionally regulate *c-fos* (Fig 3).

Role of TFII-I in Cell cycle and proliferation

TFII-I was also shown to be involved in regulating cyclin D1 that is important in cell cycle during G1-S transition. While gain-of-function of TFII-I resulted in enhanced expression of cyclin D1 and a concomitant accelerated entry to and exit from S phase, silencing of TFII-I led to cell cycle block at the G0–G1 stage with simultaneous downregulation of cyclin D1 levels (Desgranges et al., 2005). Consistent with these observations, TFII-I was recruited to the cyclin D1 promoter in vivo in response to serum stimulation and bound to the promoter in vitro. Importantly, the transcriptional induction of cyclin D1 by TFII-I was dependent on Y248 as well as Y611. Stable expression of a mutant protein carrying mutations in both sites significantly abrogated cyclin D1 expression as well as resulted in a cell cycle block at the G0–G1 stage (Desgranges et al., 2005).

It was further demonstrated that upon cell cycle block induced by genotoxic stress (γ -irradiation), TFII-I was ubiquitinated and degraded in a p53- and ATM (ataxia telangiectasia mutated)-dependent fashion. The degradation of TFII-I is 26S proteasome mediated, although the precise mechanism of degradation is currently unknown (Desgranges et al., 2005). Interestingly, sequence analysis of TFII-I protein reveals three destruction boxes of the type RXXL present at amino acids, 186–189, 206–209 and 887–890 (Desgranges et al., 2005). The RXXL destruction box motif is recognized by the anaphase promoting complex (APC) and targets proteins for proteasome mediated degradation (Jackson et al., 2000). However, whether the RXXL motif of TFII-I is functionally recognized by the APC complex and targets TFII-I for destruction is not known at present.

Further insight into the role of TFII-I during cell cycle was gained through silencing of TFII-I followed by microarray analysis and functional validation (Ashworth and Roy, 2009). Consistent with its role in regulating cyclin D1, these studies revealed that TFII-I is required for proper execution of S-phase progression and reentry into cycle as silencing of TFII-I delayed S-phase execution and entry into G2/M phase. Out of the 40,000 genes included in the array, 1793 genes were downregulated whereas 2078 genes were upregulated. Apart from cyclin D1, TFII-I regulates expression of protein kinase C- β (PKC- β) as well as several genes important for innate immune response, though the implication of this latter observation is unknown. Given that PKC- β regulates NF- κ B activity, which in turn is also required for transcriptional induction of cyclin D1, TFII-I could regulate a transcriptional network during entry and execution of S-phase. Interestingly, TFII-I was serine phosphorylated upon entry into mitosis by Cdk1, which appears to dissociate TFII-I from the condensed chromatin during prophase to pro-metaphase transition. Thus, it seems that while tyrosine phosphorylation of TFII-I is required for activation of genes necessary for G0–G1 as well as G1-S transitions, upon entry into G2/M phase, it is serine phosphorylated by Cdk1 and dissociates from the mitotic chromatin (Ashworth and Roy, 2009).

TGF- β Signaling

Apart from the mitogenic signaling pathways, TFII-I family factors also respond to TGF β /activin signaling (Ku et al., 2005). In the basal or unstimulated state, BEN is recruited to the distal element (DE) of the Goosecoid (*Gsc*) promoter together with HDAC3 resulting in downregulation of *Gsc* expression. However, upon TGF β /activin signaling, this repressive complex is replaced by TFII-I in conjunction with Smad2, leading to an induction of *Gsc* expression. Consistent with these observations, silencing of TFII-I in murine embryonic carcinoma (P19) cells results in extinction of TGF β mediated *Gsc* expression. Conversely, silencing of BEN resulted in enhanced *Gsc* expression and gain-of-function of BEN results in repression of *Gsc*. Thus, in the context of TGF β signaling, the two members of the TFII-I family transcription factors have opposing transcriptional effects (Ku et al., 2005). It should also be noted that BEN mediated activation of *Gsc* has been observed, although in this case

a truncated form of BEN was used (Ring et al., 2002). Importantly, morpholino mediated downregulation of TFII-I expression in *Xenopus* embryos led to severe defects in embryonic development. Given that *Gsc* regulates formation and patterning of embryos, TFII-I family transcription factors are likely to be important for mammalian development (Ku et al., 2005).

In a phosphoproteomic profiling study, it was discovered that TGF β signaling results in serine phosphorylation of Ser371 and Ser743 of TFII-I, further showing that TFII-I is directly downstream of TGF β pathways (Stasyk et al., 2005). Moreover, these sites are functional, as mutations in either one resulted in enhanced interaction with Smad3 and transcriptional upregulation of target genes such as cyclin D2 and E2F2. Given that Smad2 and Smad3 act upon distinct target genes (Moustakas and Heldin, 2009), these observations also suggest that TFII-I can function on both sets of target genes and therefore may be generally important for TGF β signaling pathways.

Bone morphogenetic protein (BMP) also belongs to the TGF β superfamily and controls diverse biological processes such as mesoderm patterning, left-right asymmetry, neurogenesis, somite and skeletal development, limb patterning, and the development of the kidney, gut, lung, and teeth (Zakin and De Robertis, 2010). Smad1 and Smad5 mediate transcriptional responses to the BMPs (Moustakas and heldin, 2009). In response to BMP2, cyclic guanosine 3',5'-monophosphate (cGMP)-dependent kinase I (cGKI) interacts with Smad4 and translocates to the nucleus. In the nucleus, it then binds Smad1 and TFII-I to regulate BMP target genes such as Id1 (Schwappacher et al., 2009). Thus, it appears that TFII-I is downstream of not only TGF β /activin but also BMP signaling pathways and interacts with both classes of Smads to regulate a diverse set of genes. Interestingly, the same Ser371 and Ser743 in TFII-I were also directly targeted by cGKI in response to cGMP signaling (Casteel et al., 2002; Piltz and Broderick, 2005). Whether TGF β directly targets these sites or they are indirectly targeted by cGKI in response to TGF β signaling is currently undetermined. Moreover, TFII-I directly binds to cGKI both in vitro and in vivo. This interaction is functionally relevant since cGMP mediated activation of *c-fos* is mediated by TFII-I and cGKI and cGMP analogs enhanced association between TFII-I and cGKI (Casteel et al., 2002; Piltz and Broderick, 2005). It would be interesting to test whether cGKI is co-recruited to the *c-fos* and other promoters with TFII-I and how the BMP and cGMP pathways converge to regulate gene expression through TFII-I.

Consistent with the observation that TFII-I is downstream of BMP signaling pathways, it was recently shown that TFII-I regulates osteogenic marker genes such as alkaline phosphatase and osteocalcin in response to BMP (Lazebnik et al., 2009). However, TFII-I appears to negatively regulate these genes by interfering with Runx2 recruitment. Binding of TFII-I to the osteocalcin promoter inhibited recruitment of Runx2 and pRb to the site during early differentiation. Consequently, in BMP-dependent *in vitro* osteogenic differentiation assays, silencing of TFII-I enhanced differentiation by promoting recruitment of Runx2 and pRb and upregulation of alkaline phosphatase and osteocalcin genes (Lazebnik et al., 2009).

ER stress response pathway

Several years ago, TFII-I was also identified as part of a complex that binds to endoplasmic reticulum stress response element (ERSE) and together with ATF6 was shown to activate glucose-regulated protein (Grp)78 gene (also known as BiP) (Parker et al., 2001). GRP78 is a sensor for endoplasmic reticulum (ER) stress that can be caused by a variety of physiological conditions (e.g., Ca²⁺ depletion or glycosylation block) resulting in unfolded protein response (UPR) and triggering of anti-apoptotic signaling cascades (Misra et al., 2011). Subsequent studies show that ER stress caused by Ca²⁺ depletion results in an

increase in TFII-I synthesis (Hong et al., 2005). The enhanced expression of TFII-I is well correlated with an increase in GRP78 protein expression. Moreover, ER stress also leads to enhanced TFII-I tyrosine phosphorylation at Y248 by c-Src or an Src-family kinase. Tyrosine phosphorylated TFII-I translocates to the nucleus and is recruited to the *Grp78* ERSE. Either pharmacological inhibition of tyrosine phosphorylation or mutation of the Y248 resulted in repression of *Grp78* gene expression (Hong et al., 2005).

Following these studies, it was shown that TFII-I potentiates cell survival and promotes anti-apoptotic functions in prostrate cancer cells by upregulating *Grp78* gene expression (Misra et al., 2009; Misra et al., 2011). It is known that receptor recognized forms of $\alpha 2$ -macroglobulin ($\alpha 2M^*$) bind to GRP78 and protects cells from apoptotic death. $\alpha 2M^*$ mediated cell survival and proliferation in prostrate cancer cells is caused by c-Src induced Y248 tyrosine phosphorylation of TFII-I and subsequent increase in *Grp78* expression. Thus, it is possible that activation of TFII-I via tyrosine phosphorylation and induction of *Grp78* (and possibly other stress response genes) could play a major role in UPR and pro-survival signaling pathways. Consistent with such a notion, it was further shown that apart from regulating *Grp78* gene expression, silencing of TFII-I inhibits expression of Bcl-2 and cyclin D1 and enhances expression of pro-apoptotic proteins such as p53, p27 and Bax in prostrate cancer cells. Moreover, cytoplasmic TFII-I forms a complex with phospholipase C- γ (PLC γ), transient receptor potential channel 3 (TRPC3) and caveolin to mediate ER stress response signaling (Misra et al., 2011).

Interestingly, apart from TFII-I (and ATF6), Sp transcription factors (Sp1, Sp3 and Sp4) also bind ERSE and are required for activation of *Grp78* (Abdelrahim et al., 2005). It is unclear at present whether Sp proteins promote recruitment of TFII-I and ATF6 to the ERSE, thereby enhancing transcription. Furthermore, E2F1 was also shown to negatively regulate *Grp78* expression by competitively binding to ERSE and preventing recruitment of TFII-I/ATF6 and Sp proteins to the ERSE (Racek et al., 2008). Given that *Grp78* plays an important role in pro-survival mechanism as well as drug resistance, carcinogenesis and metastasis, these observations could have important ramifications in future cancer treatment.

Calcium signaling

Desiderio and colleagues discovered an unexpected and novel role for TFII-I (Caraveo et al., 2006). While it has been known for some time that in response to extracellular ligands, receptor tyrosine kinases and G-protein coupled receptors activate various PLC isoforms to initiate calcium signaling, a novel lipase independent function of PLC- γ has also been noted (van Rossum et al., 2005). TRPC-3 cation channel regulates intracellular calcium entry by binding to PLC- γ via a pleckstrin homology (PH) domain. Although PH domains are generally believed to be important for lipid binding, a gestalt algorithm search identified split PH domains in a variety of proteins that are used for protein-protein interactions (van Rossum et al., 2005). Both PLC- γ and TRPC3 have split PH domains. Surprisingly, TFII-I also has a split PH domain, via which it interacts with PLC- γ (Caraveo et al., 2006). The split PH domain in TFII-I is in a constitutively “closed” conformation, which “opens” up upon signal induced tyrosine phosphorylation within this region. A competitive binding between TFII-I and TRPC3 to PLC- γ dictates the outcome of calcium influx. Because binding of PLC- γ to TRPC3 is essential for agonist-induced calcium entry (ACE), titration of PLC- γ by TFII-I in the cytoplasm resulted in an inhibition of ACE. Interestingly, this does not require transcriptional functions of TFII-I, as a nuclear localization deficient mutant TFII-I is fully competent in regulating ACE (Caraveo et al., 2006). However, given that the split PH domain in TFII-I is in between R1 and R2 and in close proximity to the BR and NLS, it is conceivable that binding to PLC- γ via this domain would mask the NLS in TFII-I, thereby providing an additional mechanism for its tethering to the cytoplasm under basal conditions (Roy, 2006).

Immune Signaling

TFII-I was also discovered as an interacting partner for Bruton's tyrosine kinase (BTK) in B cells (Yang and Desiderio, 1997). It was noted that TFII-I is rapidly tyrosine phosphorylated in response to B cell receptor (BCR) in a BTK dependent fashion (Yang and Desiderio, 1997; Novina et al., 1999). Because mutations in BTK are associated with X-linked agammaglobulinemia (XLA) in human and X-linked immunodeficiency (xid) in mice, these results suggested that TFII-I might have an important role in primary immune deficiency (Yang and Desiderio, 1997). It was subsequently discovered that TFII-I was tethered to the cytoplasm in association with BTK and that BCR signaling would result in BTK-mediated tyrosine phosphorylation and nuclear translocation of TFII-I. Consistent with these observations, TFII-I was found constitutively in the nucleus in B cells isolated from xid mice (Novina et al., 1999). Btk targets TFII-I at Y248, Y357 and Y462 *in vitro* (Egloff and Desiderio, 2001). One caveat is that ectopic over-expression of a potent kinase can aberrantly induce activation of secondary pathways and may obscure results. Therefore, while Y357 and Y462 are likely BTK target sites, Y248 could be activated by an Src family kinase (Egloff and Desiderio, 2001). Alternatively it is conceivable that multiple pathways could target Y248 simultaneously. Given that TFII-I is activated by a wide variety of signaling cascades in multiple cell types, a likely scenario is that distinct pathways target distinct sites in TFII-I (Roy, 2007). Consistent with this suggestion, Y248 mutant does not appear to affect BTK dependent transcriptional activation by TFII-I. Moreover, N-terminal 90 amino acids in TFII-I mediate its interaction with BTK. Although the LZ is included within this region, it appears that LZ is not directly responsible for such an interaction (Sacristan et al., 2004). Because this region is required for dimerization of TFII-I, a model is proposed in which Btk tethers TFII-I to the cytoplasm in basal state by preventing its dimerization. Upon BCR signaling, TFII-I is phosphorylated by BTK, released from the complex, dimerizes and translocates to the nucleus (Sacristan et al., 2004). Whether all cytoplasmic tethers restrain TFII-I by preventing its dimerization is currently not known.

B cell fate is determined by BCR signaling depending on the stage of development. For instance, immature B cells undergo apoptosis upon BCR engagement while mature B cells proliferate upon receiving BCR stimulation (Niiri and Clark, 2002). WEHI-231 cell lines are often used as a proxy for immature B cells as they undergo growth arrest and eventual apoptosis upon BCR or TGF β signaling. Surprisingly, silencing of TFII-I in WEHI-231 cells rendered these cells to proliferate instead of growth arrest in response to BCR or TGF β signaling (Ashworth and Roy, 2007). Rescue with ectopic TFII-I restored the growth arrest phenotype. It was shown that TFII-I regulates transcription of c-Myc. However, the regulation is indirect as TFII-I controls both c-Rel nuclear translocation as well as DNA binding by p50 homodimer. In the absence of TFII-I, c-Rel nuclear translocation is enhanced and simultaneously DNA bound p50 homodimer formation is diminished, leading to an increased formation of c-Rel:p50 (NF- κ B). While p50 homodimer inhibits c-Myc transcription, c-Rel:p50 is required for c-Myc activation. Thus, in the absence of TFII-I, c-Myc is activated in response to BCR signaling leading to enhanced proliferation (Ashworth and Roy, 2007).

TFII-I also interacts with a B-cell specific transcription factor, Bright (Rajaiya et al, 2005). Interestingly, TFII-I, Bright and Btk have been shown to form a complex and transiently associate with membrane bound lipid-rafts (Schmidt et al., 2009). Furthermore, it appears that together with TFII-I and Bright, Btk and PLC- γ also form a lipid raft associated and BCR-responsive signaling complex. Bright transiently inhibits Btk dependent tyrosine phosphorylation of TFII-I, thereby dampening the BCR response (Schmidt et al., 2009). Precisely at what point TFII-I undergoes phosphorylation and translocates to the nucleus in response to BCR signaling is yet to be determined. Once in the nucleus, Bright complexes with TFII-I and regulates transcription of immunoglobulin heavy chain (*IgH*) genes. Thus, a

mutant TFII-I that is competent in binding to DNA but lacking a putative activation region acted in a dominant negative fashion and inhibited Bright dependent transcriptional induction of *IgH*. Moreover, the Y248 in TFII-I was shown to be critical for Bright dependent transcriptional activation of *IgH*, suggesting that both DNA binding and tyrosine phosphorylation of TFII-I are required for Bright dependent induction of *IgH* (Rajaiya et al., 2005). TFII-I also interacts with chromatin remodeling factor Bam11 (a Btk associated protein and a component of the SWI/SNF ATP dependent chromatin remodeling complex) in B cells.

Several years ago, it was shown that TFII-I family proteins interact with a downstream promoter element in a subset of *IgH* promoters (Tantin et al., 2004). This element dubbed as DICE (downstream immunoglobulin control element) is important for *IgH* transcription and interaction of *IgH* promoters with corresponding enhancers (Tantin et al., 2004). A recent study provides important insight regarding the role of TFII-I in regulating *IgH* transcription (Ren et al., 2011). Regulation of *IgH* gene in mature B cells require participation of an enhancer located 3' of the *Ig* promoter region. This enhancer termed as 3'-enhancer or 3'-regulatory region (3'-RR) forms a loop with the recombined *Ig* promoter and in case of translocations with either the Bcl-2 or the c-Myc promoters (Roy et al., 2011). Transcription of *IgH* also requires octamer factors (OCT1 or OCT 2) that bind to octamer elements present in both *IgH* proximal promoter and 3'-RR and the B cell factor, OCA-B that functions as a co-activator of either OCT-1 or OCT-2. Now Roeder and colleagues show that TFII-I directly interacts with OCA-B and by virtue of binding to DICE, also recruits OCA-B to the *IgH* core promoter. These interactions are essential for looping as silencing of either OCA-B or TFII-I results in disruption of the loop formation and *IgH* transcription (Ren et al., 2011). Thus, TFII-I plays an important role in establishing enhancer-promoter communication during *IgH* transcriptional regulation (Ren et al., 2011; Roy et al., 2011).

Besides regulating B cell signaling, TFII-I can regulate T cell signaling as well (Sacristan et al., 2009). Upon triggering of the T cell receptor (TCR), several kinases, including inducible T cell kinase (ITK) are activated. Like Btk, Itk belongs to the Tec family of kinases (August, 2009). Itk interacts with TFII-I upon TCR signaling and like Btk, also phosphorylates TFII-I under these conditions. Activation/tyrosine phosphorylation of TFII-I by TCR/Itk pathway is required for induction of *c-fos* (Sacristan et al., 2009). Because SRF is required for *c-fos* activation and plays an important role in TCR responses and because TFII-I interacts with SRF, these observations suggest that TCR/Itk transcriptional responses could be mediated via TFII-I (August, 2009).

Role of TFII-I in HIV-1 transcription and virus production

Transcription of HIV-1 gene is mediated by the long terminal repeat (LTR). A variety of host cell factors interact with the LTR to potentiate HIV-1 transcription. It was shown years ago that TFII-I binds to the HIV-1 Inr element both independently and in conjunction with NF- κ B (Montano et al., 1996). In CD4+ T cells, which are the main hosts for HIV-1 in vivo, distinct signaling pathways, including the Ras/MAPK pathway, mediate viral transcription (Sadowski and Mitchell, 2005). Recent studies show that TFII-I and USF bind to several sites on the HIV-1 LTR and are downstream of the Ras/MAPK pathway in T cells (Chen et al., 2005; Sadowski and Mitchell, 2005). These elements termed RBEs are not only regulators of HIV-1 transcription but mutations in these elements result in decreased virion production and proviral expression in infected T cells. Therefore, binding of TFII-I to these elements is functional and important for HIV-1 virus production (Dahabieh et al., 2011).

A recent study remarkably shows a regulatory circuit involving TFII-I that is crucial for HIV-infection (Taylor et al., 2011). It is known that HIV-1 infection of CD4+ T cells activates genes involved in cholesterol homeostasis via sterol regulatory element-binding

protein 2 (SREBP2). TFII-I was identified as a key intermediate in this pathway. Thus, HIV-1 infection in CD4+ T cells resulted in an upregulation of TFII-I expression via SREBP2. TFII-I, in turn, potentiates Tat-dependent HIV-1 transcription. Conversely, silencing of TFII-I resulted in significantly reduced HIV-1 production in T cells. Consistent with earlier studies, TFII-I expression is enhanced upon CD4+ T cell activation via TCR ligation regardless of HIV-1 infection. Therefore, these studies imply that apart from HIV-1 transcription, TFII-I regulates cholesterol homeostasis, although TFII-I responsive genes involved in this pathway have not yet been identified (Taylor et al., 2011). Another interesting extension from these studies is that TFII-I may also control interferon response in HIV-1 infected CD4+ T cells. Microarray studies indicate that TFII-I potentially controls Interferon regulatory factor-7 (IRF-7) expression (Ashworth and Roy, 2009). Given that interferon response pathways are dysregulated upon HIV-1 infection, TFII-I might mediate interferon response during HIV-1 infection (Taylor et al., 2011).

Regulation of β -globin

While TFII-I activates transcription of several genes in response to signaling, it represses genes as well (Fig 4). Consistent with its repressive function, TFII-I physically and functionally interacts with a variety of transcriptional co-repressors viz., HDAC1 and 3, LSD1 and components of the polycomb repressor complexes (PRCs) (Crusselle-Davis et al., 2007; Hakimi et al., 2003; Tussie-Luna et al., 2002; Wen et al., 2003). Bungert and colleagues show in a series of studies that TFII-I represses β -globin gene transcription via displacement of USF and by recruiting PRC to the β -globin locus (Crusselle-Davis et al., 2006; Crusselle-Davis et al., 2007; Anantharaman et al., 2011). Although it remains unclear how USF and TFII-I regulate β -globin, they interact with each other but appear to exhibit antagonistic activities in erythroid cells. For instance, while USF activates β -globin transcription, TFII-I inhibits this gene. Consistent with these functions, USF interacts with transcriptional co-activator p300 and TFII-I interacts with Suz12 component of the PRC2 co-repressor complex. It is also possible that low concentrations of USF in erythroid progenitor cells may favor the formation of heterodimers with TFII-I, thereby contributing to the repressive activity of TFII-I. However, upon differentiation, enhanced USF concentrations might lead to the formation of USF homodimers, which activate erythroid cell-specific gene expression patterns (Crusselle-Davis et al., 2006; Crusselle-Davis et al., 2007; Anantharaman et al., 2011). Interestingly, TFII-I is recruited broadly within the transcribed α -globin gene and its recruitment pattern mimics that of an elongation factor FACT, suggesting that TFII-I may play a role in the process of transcription elongation or at least at a post-initiation step (Vernimmen et al., 2007). Thus, it is possible that TFII-I may switch from a repressive role to an activating role during the differentiation of erythroid cells (Anantharaman et al., 2011). Based on these observations, it is likely that TFII-I has an important role in regulating globin gene transcription and erythroid differentiation.

TFII-I and Disease connection

An interesting study that further addresses the role of TFII-I as a transcriptional repressor looks at Src-transformed cells (Bu et al., 2011). The SSeCKS/Gravin/AKAP12 gene is associated with metastasis suppressing activity. It is downregulated in Src-transformed cells via recruitment of HDAC1 to a promoter site that is normally occupied by USF and Sp1 and Sp3 factors. This site is also occupied by TFII-I in Src-transformed cells and Src-mediated tyrosine phosphorylation of TFII-I enhances this recruitment and its interaction with HDAC1, thereby contributing to the repressive function (Bu et al., 2011). However, it is unknown whether TFII-I forms a heterodimer with USF under these conditions (as shown at the β -globin promoter). Moreover, how Src-mediated tyrosine phosphorylation contributes to activation of TFII-I upon growth factor stimulation or ER stress (Cheriyath et al., 2002; Hong et al., 2005), while it leads to its suppressive function in SSeCKS regulation remains

unclear. Nevertheless, given that SSeCKS is a tumor suppressor, its down regulation by TFII-I via an Src-dependent pathway could have important biological ramifications (Bu et al., 2011).

TFII-I dependent repression of estrogen-responsive genes via interactions with estrogen receptor α (ER α) has been shown in a breast cancer cell line (Ogura et al., 2006). These studies show that TFII-I is constitutively recruited to the Inr element of estrogen-responsive genes (*cyclin D1* and *pS2*) but not to genes lacking an Inr element (e.g., *HSP70* and *GREB1*). Moreover, TFII-I also directly interacts with ER α and corepressors HDAC1 as well as SMRT. Accordingly, silencing of TFII-I led to an increase in expression of Inr-containing estrogen responsive genes. Because many of these are pro-proliferative genes, inhibition of TFII-I accelerated cellular proliferation. This effect is due to an increase in S-phase cells, which is also observed in WEHI-231 B cells (Ogura et al., 2006). The authors further note some similarities between TFII-I and BRCA1, the product of the tumor suppressor gene that is frequently mutated in breast and ovarian cancers (Ogura et al., 2006). For instance, like TFII-I inhibition, suppression of BRCA1 expression in breast or ovarian cancer cells leads to estrogen-independent overgrowth and to estrogen-independent transcriptional up-regulation of estrogen-responsive genes (Zheng et al. 2001). Moreover, in gain-of-function experiments of BRCA1, growth retardation in various cell types including MCF-7 cells was noted (Ogura et al., 2006). Finally, like TFII-I, BRCA1 also directly interacts with ER α (Ma et al. 2005). Therefore, it is possible that BRCA1 and TFII-I may play similar but non-redundant roles regulating of ER α dependent transcription (Ogura et al., 2006).

A recent report indeed connects the two proteins by showing that TFII-I directly interacts with BRCA1 via the BRCT domain of the latter (Tanikawa et al., 2011). This study shows that BRCA1 acts as a transcriptional co-factor for TFII-I and activates the expression of several target genes including SIRT1 and tumor suppressor p53 that are involved in DNA damage checkpoint pathways. Consistent with this observation, TFII-I was found to be co-localized in nuclear foci with BRCA1 upon γ -irradiation induced DNA damage. Thus, on the one hand TFII-I might inhibit expression of pro-proliferative genes in breast cancer cells thereby inhibiting tumor growth and on the other hand activate tumor suppressor genes resulting in inhibition of cellular proliferation (Tanikawa et al., 2011). Additionally, these results implicate TFII-I in DNA damage response pathway, although the potential mechanism of how this could be achieved remains unknown (Desgranges and Roy, 2006; Tanikawa et al., 2011).

Dysfunction of pancreatic β -cells is associated with type 2 diabetes. DJ-1 (*park7*) is a multifunctional protein involved in Parkinsonism and neuro-protection in response to oxidative stress (Inberg and Linal, 2010). It is also involved in glucose metabolism in β -cells in response to oxidative and ER stress. TFII-I was shown to be an interacting partner of DJ-1 and such interactions retained TFII-I in the cytoplasm thereby dampening its transcriptional functions. Therefore, regulating nuclear translocation of TFII-I could modulate glucose metabolism in response to oxidative and ER stress in pancreatic β -cells (Inberg and Linal, 2010).

TFII-I and Regulation of Angiogenesis

It was known for quite some time that TFII-I regulates vascular endothelial growth factor receptor-2 (*VEGFR2*) gene (Wu and Patterson, 1999). VEGFR2 (Kdr/Flk1) functions as the primary mediator of VEGF signaling in endothelial cells and therefore regulates angiogenesis. TFII-I binds to the Inr element of the *VEGFR2* gene both *in vitro* and *in vivo* and silencing of TFII-I results in decreased *VEGFR2* expression (Jackson et al., 2005; Wu and Patterson, 1999). While these reports show that TFII-I activates *VEGFR2* via the Inr

element, a recent report shows that TFII-I suppresses *VEGFR2* expression and consequently angiogenesis (Mammoto et al., 2009). This study shows that p190RhoGAP controls capillary network formation in vitro in human microvascular endothelial cells and retinal angiogenesis in vivo by modulating the balance of activities between TFII-I and GATA2 that govern transcription of *VEGFR2*. Thus, cytoplasmic retention of TFII-I by p190 results in activation of *VEGFR2* expression, while retention of GATA2 results in its inhibition. Importantly, this novel angiogenic pathway is sensitive to both mechanical (extracellular matrix elasticity mechanical) as well as chemical (soluble VEGF) stimuli (Mammoto et al., 2009).

In Matrigel assays, silencing of TFII-I altered cell infiltration and capillary vessel formation. Importantly, silencing of TFII-I in neonatal (P14) mouse retina drastically altered vessel formation. Similar effects were observed in earlier (P5) retina, containing rapidly growing microvessels. Conversely, over-expression of TFII-I caused decreased vascular density in retina (Mammoto et al., 2009). These data clearly show that TFII-I is essential for control of angiogenesis in vivo. Although the exact reason as to why in some instance TFII-I activates *VEGFR2* while in other instance it inhibits the same gene is presently unclear, one possible reason could be that the Ingber studies utilized endothelial cells of microvascular origin (Mammoto et al., 2009) and the other studies (Jackson et al., 2005; Wu and Patterson, 1999) used cells of macrovascular origin. In addition, it is also possible that the distinct isoforms of TFII-I might play a role in regulating *VEGFR2* expression. Further studies are required to resolve this issue.

Role of TFII-I in WBS

WBS is a multisystem dysfunction that includes supraaortic stenosis (SVAS), hypercalcemia in infancy, mild to moderate mental retardation, cognitive defects, and characteristic craniofacial abnormalities (Pober, 2010). It is caused by a hemizygous deletion of 25–30 genes on chromosome 7q11.23. The frequency of this genetic haploinsufficiency is estimated to be 1 in 20,000 live births (Pober, 2010). Although most cases are sporadic, WBS is inherited as an autosomal dominant trait in some families (Pober, 2010). Because the complex features of WBS are ultimately due to the decreased copy number of several genes, the critical downstream biological pathways that alter development and adult function remain difficult to dissect. All three TFII-I family genes are deleted in typical WBS patients (Pober, 2010). However, rare individuals with smaller deletions in the WBS region have been identified (Dai et al., 2009; Edelman et al., 2007). Analyses of these atypical patients have started to yield a genotype-phenotype correlation map. For instance, SVAS is strongly correlated to the Elastin (*El*) gene (Pober, 2010) and hemizygosity of *GTF2I* likely contributes to mental retardation and social behavior such as increased gaze and attention to strangers (Dai et al., 2009; Hirota et al., 2003; Morris et al., 2003). TFII-I family genes are highly expressed in normal neuronal tissues and exhibit extensive cytoplasmic expression in Purkinje cells (Danoff et al., 2004). Thus, it is likely that alterations in the levels of TFII-I observed in WBS might be responsible for neurocognitive deficits. Interestingly, transcription functions of TFII-I have also been implicated in dyslexia (Tapia-Paez et al., 2008). However, the precise molecular mechanisms and pathways via which TFII-I might control neurophysiology of WBS are still unclear.

Consistent with a pleiotropic role of TFII-I, mice homozygous in *Gtf2i* allele exhibit embryonic lethality, which is accompanied by severe defects in vasculogenesis and angiogenesis with concomitant down-regulation of *VEGFR2*, suggesting that TFII-I activates *VEGFR2* in vivo (Enkhsandakh et al., 2009). Embryonic hemorrhage of the mutant embryos was apparent at E10.5. The incidence and severity increased during development, and at E12.5, over 60% of embryos suffered serious bleeding. The mutant embryos were pale and showed arrested growth at E9.5 suggesting the possibility of

defective hematopoiesis in both the embryo body and the yolk sac due to defects in blood vessel formation (Enkhtandakh et al., 2009). The expression of TFII-I during post-implantation murine embryonic development shows interesting features that are consistent with its role in early development. For instance, although TFII-I is expressed throughout the period from E8–E16, its localization during this period shifts from cytoplasmic to predominantly nuclear. It is highly expressed in neuronal precursors at stage E8 (Fijalkowaska et al., 2010).

Although homozygosity in *Gtf2i* results in embryonic lethality, a subset of *Gtf2i*^{+/-} heterozygous mice exhibited retarded growth, kyphosis, and craniofacial defects (Enkhtandakh et al., 2009). These results show that haploinsufficiency in *Gtf2i* (TFII-I) may account for the craniofacial and skeletal abnormalities observed in WBS. It is also worth noting that there are several reports indicating spinal defects, scoliosis and kyphosis associated with some WBS patients, suggesting that in addition to the characteristic craniofacial abnormalities, these patients likely exhibit more general skeletal/bone defects (Enkhtandakh et al., 2009). Consistent with these findings, TFII-I has been implicated in murine odontogenesis (tooth development) as it is expressed highly in developing teeth compared to the surrounding tissues (Ohazama and Sharpe, 2007). Bayarsaihan and colleagues have identified several TFII-I target genes that are potentially involved in craniofacial defects and therefore could explain some of these phenotypes. Moreover, these analyses also revealed that TFII-I potentially regulates a number of genes that encode modifiers of histones and chromatin, which might explain its general role in animal development (Chimge et al., 2008; Makeyev and Bayarsaihan, 2009; Makeyev and Bayarsaihan, 2011).

Future perspectives

While the last decade has provided significant insight into biological functions of TFII-I and identified its various interaction partners (Fig 5), clearly a lot more knowledge needs to be gained. For instance, what are the target genes of TFII-I and are they the same in different cells and under different signaling conditions? Does it only participate in transcription initiation or does it also participate at a post-initiation step? TFII-I functions both as a transcriptional activator as well as a repressor (Fig 4). Although these are likely to be promoter context dependent and partner interaction dependent, what parameters precisely determine which function is manifested and under what conditions? Knock out of TFII-I clearly shows its biological importance. However, given the early embryonic lethality, its predominant biological role and mechanism of action remains unknown. Generation of conditional knockout alleles in particular cell types might resolve some of these issues. Finally, the role of TFII-I in neurocognitive phenotype seen in WBS patients needs to be critically evaluated. I fully anticipate that the next decade will provide many of these answers and firmly establish the mechanism of action as well as biological functions of this highly interesting transcription factor.

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Highlights

- Here I discuss recently discovered properties of the transcription factor TFII-I
- TFII-I family factors all have unique repeated domains
- NMR structure of a TFII-I repeat domain is solved and shows a unique fold
- TFII-I is important for promoter-enhancer communication
- TFII-I is implicated in cancer, angiogenesis and neurocognitive development

Figure 1. Structural Features of TFII-I

a) Schematic of TFII-I with 6 repeated regions, R1–R6, the N-terminal leucine zipper (LZ) and the basic region (BR) which serves as a DNA binding domain. B) The sequence of the repeats R1–R6. The most conserved amino acids are indicated in bold and the I-repeat is underlined. c) Both the linear arrangement and NMR structure of the murine repeat 5 (R5). The various amphipathic helices are indicated as $\alpha 1$ – $\alpha 4$ and the beta sheets are indicated as $\beta 1$ and $\beta 2$. The figure depicting the NMR structure is kindly provided by H. Hirota. This unique structural fold is referred to as an I-fold.

Figure 2. Schematic of the TFII-I family transcription factors

TFII-I, also known as GTF2I has 6 repeats (R1–R6) with the NLS and BR preceding R2. BEN (GTF2IRD1/MusTRD1/GTF3) has five repeats with the NLS located toward the C-terminal region. The S-S is a serine stretch, the precise function of which is unknown. The third member, GTF2IRD2 has only two repeats (R1 and R2) and does not have any NLS. The N-terminal region of this member shares 75% identity with TFII-I and resembles a truncated TFII-I. GTF2IRD2 has a Charlie8 transposon-like domain. However, the function of this domain is currently unknown. The N-terminal leucine zipper (LZ) is well conserved amongst the three members.

Figure 3. Growth factor signal induced regulation of transcription by the two isoforms of TFII-I
 (A) In basal state, unphosphorylated TFII-IA is predominantly cytoplasmic, tethered by p190RhoGAP (p190). Other molecules can also tether TFII-I in the cytoplasm (not shown for simplicity). TFII-IB is recruited to a *c-fos* promoter site, likely in conjunction with co-repressors (red) (e.g., HDAC1 and 3, LSD1 or PRC) resulting in a transcriptional repression.
 (B) Upon signaling, TFII-IA undergoes phosphorylation, interacts with Erk1/2 and translocate to the nucleus. Under these conditions, TFII-IB is exported out of the nucleus and instead TFII-IA occupies the same site on the *c-fos* promoter, resulting in transcriptional activation. It is conjectured that under these conditions, TFII-IA interacts with transcriptional co-activators (green), although the precise identities of these factors are currently unknown.

Figure 4. Signal dependent activation and repression mediated by TFII-I

Shown on the left, signal -dependent transcriptional repression mediated by TFII-I (in red). The target genes and functional consequences are indicated. Shown on the right, signal-dependent transcriptional activation mediated by TFII-I (in green). These functions are likely to be signal and cell type dependent as activation and repression of both VEGFR2 and cyclin D1 have been shown.

Figure 5. Interacting partners of TFII-I

The interacting proteins are divided into four functional groups: transcription factors/co-factors, chromatin modifying factors, histone modifying factors and signaling molecules. These interactions are observed in different cell types and under distinct conditions.