Regulation of the Ets transcription factor Tel

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CHAPTER 5

General Discussion

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The Ets family of transcription factors is one of the largest families of transcription factors and they have been intensively studied for their central roles during development and disease. Tel is unique in the family in being a dedicated repressor of gene expression. The majority of studies have focused on its role in cancer in which it has been found to be part of at least 40 different chromosomal translocations involving up to 22 different genes (1). The work in this thesis has aimed to elucidate the mode of action of this transcription factor. By taking an evolutionary approach, simultaneously studying Tel and its invertebrate counterpart, Yan, in a variety of species, we have uncovered fundamental aspects of Tel/Yan regulation.

Posttranslational control of the pool of Tel/Yan proteins

Despite its critical role in development coupled to its clinical importance there is a relative lack of mechanistic insight into its function. Over the years a model has emerged that envisions the transcriptional repressors Tel and Yan to exist in a dynamic equilibrium of monomers and DNA bound oligomers. Deciphering the mechanisms that guide transitions between these forms is of major importance for understanding Tel/Yan function. In *Drosophila*, the protein Mae (Modulator of the Activity of Ets) fulfills a crucial role to control the balance between actively repressing oligomeric Yan and the monomeric forms. Mae sensitizes Yan for MAPK-mediated down regulation and negatively regulates oligomeric repression via depolymerization. By binding to monomers it also prevents overt nuclear export by inhibiting access of the exportin Crm1 to Yan. A pool of Mae-bound Yan monomers are subsequently available to be either exported or to be incorporated into (DNA bound) oligomers (2-6).

A mammalian Mae gene has not been identified; our studies on regulation of Tel by SUMO as described in chapter 2 indicate that functionally, SUMO controls the balance between repressive and nonrepressive forms of Tel. We found that SUMOylation on lysine 11 (K11)

serves to limit DNA binding of Tel and thus inhibits repression. In cells SUMOylation of oligomers is stable, but SUMOylation of monomers seems to sensitize them for degradation. Importantly, this was one of the first demonstrations that SUMOylation can sensitize proteins for proteasomal degradation. It appears Tel function can be readily adjusted according to a particular need as a pool of SUMOylated oligomers can be (rapidly) mobilized to the DNA and affect repression of target genes. A prerequisite here is that these SUMOylated Tel proteins are deSUMOylated, which implies a crucial role for SUMO-proteases in the regulation of repression by Tel. Indeed we have found that the family of SENPs can induce deSUMOylation of Tel (Roukens & Baker unpublished data). Alternatively, the pool of SUMOylated Tel can be monomerized leading to its subsequent degradation.

The fact that SUMOylated monomers are sensitized for degradation, coupled to the fact that Yan appears to be actively degraded as it is absent in differentiated cells, suggested that degradation could play an important role in regulating Tel/Yan function. Significantly, in yeast-2-hybrid screens we identified the F-box protein Fbl6 as a common interacting protein for both Tel and Yan. Since F-box proteins are the substrate recognition modules in the SCF (for Skp-Cullin-F-box) complexes, which serve as ubiquitin E3 ligases, this implied that Tel and Yan are subject to ubiquitin mediated degradation. Indeed the findings in Chapter 3 establish that Fbl6 mediated ubiquitination is an important evolutionarily conserved mechanism of downregulation of Tel and Yan.

The fact that Tel is degraded exposed a novel angle into its downregulation, since Tel is a relatively stable protein. We found that Tel is ubiquitinated in cells and that this process was stimulated by Fbl6. Consistent with our findings in chapter 2 we found that monomeric forms of Tel were particularly labile, and were strongly ubiquitinated. This supported the idea that SUMOylation sensitizes monomeric Tel for degradation via the ubiquitin/proteasome system. These findings were among the first to highlight crosstalk between SUMOylation and ubiquitination in the regulation of a target protein. Indeed the idea of coregulation by SUMOylation and ubiquitination has garnered major interest since and for many proteins it has been subsequently found that SUMOylation can stimulate proteasomal degradation (7). In the case of Tel, this interplay appears to be specific to

monomeric forms of Tel. It raises the intriguing possibility that SUMOylated monomers are more accessible for binding by Fbl6, leading to their subsequent degradation.

Interestingly we have also found that other Ets factors, such as Fli-1, Erg and Tel2 are SUMOylated and that the SUMOylated fraction is strongly stabilized upon proteasomal inhibition (Roukens and Baker, unpublished data). As we have also found that Tel2 is ubiquitinated by Fbl6 it will be interesting to study whether cooperation between SUMOylation and F-box mediated degradation is a more general strategy to regulate the stability of Ets factors.

Proteasomal degradation was not restricted to Tel, but was also shown to be relevant for Yan regulation. Previous studies have implicated that Yan is degraded, but this had not been formally demonstrated (8).We have shown that Fbl6 mediated ubiquitination serves to downregulate Yan protein in cells and *in vivo*. However, it appears that Yan is downregulated by multiple complementary mechanisms. This can be inferred from the following: proteasomal inhibition was unable to fully rescue degradation induced by Mae and Ras, suggesting a concommittant proteasome independent mechanism of downregulation. This may reflect the role of nuclear export which subsequently leads to inactivation of Yan. Since ubiquitination of Yan via Fbl6 mainly occurs in the nucleus it is likely that these form two separated pathways of downregulation that may both be stimulated by Ras/MAPK/Mae activity. It is also possible that Fbl6 finetunes Yan activity in the nucleus in absence of phosphorylation, whereas activation of MAPK phosphorylation then stimulates a strong degradative response that downregulates Yan via both mechanisms.

CtBP is a crucial component of the Tel complex

The posttranslational modifications by SUMO and ubiquitin control the pool of Tel/Yan that is available for repression. As mentioned in Chapter 1 repression might be achieved via multiple mechanisms. This involves the formation of homotypic oligomers that block access of transcriptional activators. However, another crucial aspect is the recruitment of corepressors which are instrumental in mediating repression. A greater understanding of the

interplay between Tel and its corepressors is pivotal for determining how Tel mediates repression of its target genes.

Our work presented in Chapter 4 has added a new dimension for understanding how repression by Tel is regulated specifically through recruitment of the generic corepressor C-terminal Binding Protein (CtBP). Our evolutionary approach again proved to be invaluable as we identified a CtBP binding motif in the amino acid sequence of Yan. A highly similar sequence was conserved in all Tel proteins in vertebrates and was indeed found to be indispensable for binding of CtBP by Tel. In the ensuing studies we found that CtBP is integral to Tel function and appears to regulate stable nuclear complex formation. CtBP stabilizes Tel protein levels and the deletion of the CtBP binding motif in Tel induces mislocalization into the cytoplasm. It stably associates with oligomers but not with monomers, which may indicate that CtBP reinforces the formation of Tel oligomers. The fact that CtBP can dimerize may provide a mechanism that can further regulate the nature and extent of the oligomer; perhaps a CtBP dimer can connect two ends of a oligomeric Tel complex, and thus effectively induce the formation of a closed oligomer. This may further limit depolymerization or degradation as CtBP forms a barrier for access of SUMO, Fbl6 or any other factor leading to a loss of DNA-bound Tel. Similarly in this context CtBP could act antagonistically to Mae in *Drosophila*. Structural studies should be employed to determine exactly how the Tel:CtBP complex is ordered and this may shed light on the mechanism of how CtBP regulates Tel stability.

A major implication of the link with CtBP is that Tel function is sensitized to the metabolic status of the cell, since CtBP has been postulated to be a redox sensor (9,10). Indeed we find that metabolic alterations can strongly affect Tel protein stability and this is of particular interest in processes such as angiogenesis or tumor progression where metabolical conditions may be highly altered. This will be further elaborated upon below.

Our results have thus placed CtBP as a corepressor of major importance in the regulation of repression by Tel. There are two different vertebrate *ctbp* genes encoding the CtBP1 and CtBP2 proteins, which exhibit a high degree of sequence homology. We have shown that CtBP2 is preferentially associated with Tel and that CtBP1 can even inhibit binding of CtBP2 to Tel. This is a first demonstration of differential binding of a target by CtBP1 and

CtBP2. This finding further illustrates that corepressors may regulate the recruitment of other cofactors by transcription factors. Numerous reports have previously highlighted the importance of corepressor recruitment by Tel (11-16), but it is currently unclear what the interplay between these various corepressors is. It will be of great interest to determine whether other corepressors, such as mSIN3A, NCOR and SMRT will similarly exhibit hierarchical recruitment and whether they affect or are affected by CtBP.

Regulation of angiogenesis by Tel

Since *Drosophila* Yan is an important mediator of tracheal branching (see Chapter 1), a process which shares many molecular mechanisms with angiogenesis, and loss of Tel is associated with a yolk sac angiogenesis defect (17), we hypothesized that Tel would also be a central regulator of angiogenesis. Interestingly, the CtBP2 knockout mice exhibit a similar lack of vitelline vessels. For many years the underlying mechanism of the angiogenesis defect in Tel knockout mice had remained elusive, but our work in Chapter 4 shows that Tel acts directly in endothelial cells, that it controls endothelial cell sprouting and provides the mechanism by which this is achieved. Moreover, we show that its activity during endothelial sprouting is dependent on CtBP. Importantly, we found that Tel is the crucial transcriptional link between pro-angiogenic Vascular Endothelial Growth Factor (VEGF) signaling and the intercellular anti-angiogenic Delta-like 4 (Dll4)/Notch pathway. In endothelial cells a pulse of VEGF leads to a transitory loss of the Tel:CtBP complex at the DNA, which allows target genes such as *dll4* to be derepressed. The increase in *dll4* expression guides a regulated formation of a sprout by determining tip/stalk cell fate and prevents excessive sprouting. Besides the prominent effect on *dll4* expression Tel similarly regulates the repression of many other angiogenic genes; by constraining the expression of these downstream targets Tel controls the stringency of the transcriptional response to VEGF, ensuring that genes required for angiogenesis are only activated once VEGF signaling is activated beyond a certain threshold. The transient nature of the dissociation of the Tel complex further ensures that these genes are activated for a defined period of time, which provides a refined control over the growth of the forming blood vessel. By these

mechanisms Tel is instrumental in the regulation of the position, length and integrity of the new sprout that forms.

This process by which Tel mediates angiogenesis is reminiscent of the way that Yan regulates tracheal development which requires inhibition of Yan via receptor tyrosine kinase (RTK) FGF signaling (18). But the regulation of Tel by RTK signaling appears to be fundamentally different to the reported effect of RTK signaling on Yan. It was suggested that RTK signaling triggers Yan down regulation; however RTK signaling in endothelial cells does not alter Tel protein levels but does alter the timing of its action. Since the transitory dissociation of the Tel:CtBP complex occurs rapidly (within minutes) after activation of VEGF signaling it is likely that the loss of the complex is driven by posttranslational modifications of Tel (or CtBP). VEGF signaling activates a variety of different kinases which may phosphorylate Tel, leading to a loss Tel DNA-binding. In contrast with Yan, however, Tel does not get (permanently) downregulated but is, in time, reconfigured into a repressive complex. This temporary dissociation from the DNA may well be further regulated by SUMOylation of Tel, which presumably has evolved for such a purpose, i.e. to create a pool of Tel that can be readily mobilized for repression.

Thus, by temporarily inactivating Tel, VEGF affects transitory phases of derepression of angiogenic genes. These genes are certainly subject to multiple layers of regulation and their upregulation following VEGF signaling will likely be enhanced by transcriptional activators. It will be of great interest to identify activators of these genes that will further guide the phase of transcriptional activation. Some transcriptional activators will likely bind to similar promoter elements as Tel, and they will therefore compete for these common binding sites. This concept of competition is known for a variety of contexts in *Drosophila*, where Yan and Pointed bind to common Ets Binding Sites (19-21). In vertebrates such a clear relationship between Tel and an activator has not been identified. A similar competition may exist between Tel and other Ets transcriptional activators such as Ets 1 and/or Fli1, both of which have been suggested to be required for angiogenesis (22,23).

The relationship with Fli-1 will be of particular interest since Tel and Fli-1 not only share a role in angiogenesis, but are also both required during hematopoiesis. A number of studies have shown that these Ets factors both affect promoters of megakaryocyte specific genes,

but in an opposing manner, but these studies have lacked mechanistic insight. An intriguing aspect of this relationship is that Fli-1 has been reported to interact with Tel (24, 25). Perhaps the binding serves to keep Fli-1 in an inactive form, but readily available to activate the genes once the barrier of Tel repression is relieved by VEGF signaling. Alternatively, Fli-1 may be a context dependent transcription factor, acting as a (co)repressor when bound to Tel. Our work on the role of Tel in angiogenesis provides an excellent base to explore the putative functional relationship between Tel and Fli-1 in this process.

Other biological roles of Tel

The work in chapter 4 has provided strong insight into how Tel regulates angiogenesis. These findings may provide indications of how Tel acts in other biological processes as well. For example, the interplay between signaling pathways and Tel function has not been well characterized. The work showing that VEGF signaling regulates Tel function is the first demonstration of how Tel is regulated by RTK signaling during development. By contrast, it is well established that signaling via RTKs can downregulate Yan and how this might drive development in *Drosophila* is reasonably well understood. Only a limited number of highly conserved signaling pathways have evolved that are used repeatedly to pattern all, or at least most, tissues. RTK signaling is one such pathway that regulates cell fate. In *Drosophila*, inhibiting Yan function appears to be an essential function of this pathway (8, 26-29). Since we have found that Tel functions to regulate the response of endothelial cells to VEGF signaling and many molecular regulations are highly conserved between Tel and Yan, it is not inconceivable that Tel, like Yan, is a target of multiple RTK signaling pathways. Moreover the fact that Tel is widely expressed also implies that it might regulate fundamental cell signaling events. For example, it is well established that Tel is essential for postnatal bone marrow hematopoiesis, by regulating survival of hematopoietic stem cells (HSC), but the mechanism by which Tel regulates HSC survival is unknown (30). Perhaps Tel will play a similar role in HSC survival by transcriptionally linking RTK signaling to the Notch pathway, which may serve to keep HSCs primed for differentiation.

Another area that has remained underexplored for Tel is its role in the development of the nervous system. In mice Tel exhibits particularly high expression in the cranial nerve ganglia, the dorsal root ganglia and in the ventral region of the caudal neural tube (17). Moreover the role of Yan in photoreceptor development is well characterized and loss of Yan flies exhibit strong defects in the medial parts of the brain (8,26,28). One interesting possibility is that Tel is involved in axonal guidance. Like the endothelial cell response to VEGF, neuronal growth is guided by a variety of guidance molecules. The migration of the growing axon further mirrors endothelial sprouting as it is led by a highly motile 'tip cell' called the growth cone (31). Our work has demonstrated that Tel is crucial for interpreting the VEGF signals in endothelial cells. By upregulating Dll4 expression Tel also inhibits tip cell characteristics in the stalk cells. In tumor cells, Tel was also found to inhibit focal adhesions (32), which may suggest that one of the features of Tel is that it inhibits enhanced motility of leading edge cells. Perhaps Tel could similarly affect axonal growth cones, by ensuring a regulated response to guidance cues and inhibiting the growth cone phenotype in trailing cells.

Finally, the role of Tel in cancer progression is of major importance. Until now Tel has mostly been recognized as a causative agent in leukemias involving translocations of Tel. On the other hand studies in recent years have highlighted a possible role for Tel as a tumor suppressor (1). The data that we present indicates a more complicated involvement of Tel in tumor growth since Tel is indispensable for endothelial sprouting. Crucially, this exposes a novel mechanism by which Tel can actually promote tumor growth, via regulation of tumor angiogenesis. Angiogenesis is a key process in tumor progression, as tumors require active delivery of nutrients and oxygen via blood vessels to grow beyond a few millimeters in size. For this tumors signal to the local vasculature to stimulate aberrant angiogenesis. It is becoming increasingly clear that the tumor microenvironment plays an important instructive role in tumor angiogenesis. The tumor microenvironment is chemically and metabolically heterogeneous; local areas of hypoxia and high concentrations of lactate are generated because of the (initial) lack of vasculature and the high metabolic rate of tumors. These properties appear to stimulate tumor angiogenesis but how the tumor microenvironment affects transcriptional effectors of angiogenesis is ill-defined. Our finding that Tel function is linked to the redox sensor CtBP may prove to be central to

define this mechanism, as it indicates that Tel activity is critically dependent upon metabolic status. Indeed we find that hypoxia and lactate, which are abundant in the tumor microenvironment, can strongly stabilize Tel protein levels, which may subsequently stimulate tumor angiogenesis. It will be of great importance to test this hypothesis *in vivo*, and determine whether Tel is upregulated in tumor-associated endothelial cells. Importantly, this places Tel as a potential new target to inhibit tumor growth therapeutically.

Concluding remarks

The work in this thesis has provided substantial insight into how Tel and Yan are regulated. SUMOylation of Tel on K11 and Fbl6-mediated ubiquitination control the balance between repressive and nonrepressive forms. These processes underscore the importance of posttranslational regulation of these transcription factors. In contrast, recruitment of the generic corepressor CtBP is required for stable Tel complex formation. Crucially our work unraveled mechanistically how Tel mediates angiogenesis. Arguably the greatest conceptual insights in this thesis have resulted from taking an evolutionary approach, which has directed this work towards many important conserved aspects of Tel/Yan function. Future studies will greatly benefit from an additional model system that we have recently employed (Chapter 4), namely the zebrafish, *Danio Rerio*. The zebrafish is genetically tractable, it is a vertebrate with a very short development time, and using reverse genetics allows the study of Tel during early development. We have already shown that Tel is crucial for vascular development in zebrafish and this powerful model system should yield more insight into Tel biology in the future.

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