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Review

The transcription factor *Fos*: a Janus-type regulator in health and disease

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Summary. The immediate early gene product *Fos* is part of the activator protein-1 (AP-1) transcription factor and has been shown to participate in the molecular mechanisms of cell proliferation, differentiation, apoptosis, and transformation. The analysis of genetically modified mice and cells derived thereof has provided important new insights into its specific biological functions in development, tissue homeostasis, and cellular responses to environmental insults. Moreover, the deregulation of *Fos* could be linked with a variety of pathological conditions, including immunological, skeletal and neurological defects, as well as oncogenic transformation and tumor progression. In contrast to the mainstream opinion concerning the oncogenic function of Fos an increasing number of experimental reports also describe a tumor-suppressive function in various cancer types. More recently, altered Fos expression in cell culture and mouse models combined with global gene expression analysis unraveled novel downstream effectors of the Fos-regulated genetic program. Finally, selective inhibition of its function with a small molecule inhibitor in a preclinical mouse model of arthritis demonstrated that targeting Fos/AP-1 activity could be an auspicious new option for clinical use.

Key words: AP-1, Bone, Cancer, CNS, Oncogene

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Introduction

Fos was initially identified as a viral oncogene (*v-Fos*) from murine osteosarcomas whose expression resulted in cell transformation (Curran et al., 1983; Van Beveren et al., 1983; Angel and Karin, 1991). The cellular *Fos* homologue (also known as *c-Fos*) was among the first immediate early genes to be identified and shares all characteristics of this group of genes: (i) low or undetectable expression in quiescent cells, but rapid transcription in response to many extracellular signals, (ii) transcriptional induction is transient and independent of new protein synthesis, and (iii) specific transcript with very a short half-life that encodes a protein with high turnover. The Fos protein preferentially forms heterodimers with members of the Jun protein family (Jun, Junb, Jund) to acquire transcriptional competence (Angel and Karin, 1991; Shaulian and Karin, 2002). As Fos/Jun heterodimeric complexes recognize the so-called TPA-responsive element (TRE = TGA$^{G}/_{C}$TCA) that is found in the regulatory units of many genes, Fos is involved in the regulation of a large variety of physiological processes. At the cellular level, Fos regulates proliferation, differentiation, cell death, and response to environmental cues, and in organisms Fos plays paramount roles in organogenesis, immune response, congenital functions, among others (Wagner, 2001; Eferl and Wagner, 2003; Hess et al., 2004).

The *Fos* gene is subjected to complex regulation at multiple interwoven transcriptional and post-transcriptional levels, which is necessary to avoid, or at least limit, pathological effects caused by its deregulation (Shaulian and Karin, 2002; Lee et al., 2006). In particular, MAP kinase signaling pathways play a fundamental role in the activation of both Fos transcription and protein activity (Treisman, 1995; Cahill

et al., 1996b; Murphi et al., 2002; Shaw and Saxton, 2003; Chalmers et al., 2007; O'Donnell et al., 2008). However, pre-existing or newly synthesized Fos protein is not only modified by phosphorylation, but also by ubiquitinylation and sumoylation regulating its transcriptional activity, its sub-cellular localization and its turnover (Papavassiliou et al., 1992; Acquaviva et al., 2002, Murphy et al., 2002, Ferrara et al., 2003, Bossis et al., 2003, 2005; Sasaki et al., 2006; Basbous et al., 2007, 2008). In addition, Fos activity is modulated by physical interactions with other transcription factors, co-factors, and other nuclear proteins (Wagner, 2001; Kassel et al., 2004; Ivorra et al., 2006; Gonzalez et al., 2008).

Fos function in normal development and pathophysiological condition

Many important insights regarding the specific function of Fos protein in development and disease have been obtained from genetically modified mice (Tables 1 and 2) and cells derived thereof (Hess et al., 2001; Wagner, 2001). Mutant mice with homozygous *Fos* deletion (*Fos*$^{-/-}$) exhibited a significant loss of viability at birth and only 40% survive and grow at normal rate until they develop severe osteopetrosis. Among other abnormalities these mice showed altered haematopoiesis and behavior (Johnson et al., 1992, Wang et al., 1992).

Immune system development and function

In Fos-deficient mice, B cell numbers were reduced in the spleen, lymph nodes and the peripheral blood as a result of a marked reduction in the number of clonogenic B cell precursors. However, *in vitro* differentiation and bone marrow reconstitution experiments demonstrated that haematopoietic stem cells lacking Fos have full developmental potential and that the observed defect in B cell development is most likely due to the impaired bone marrow environment as a consequence of osteopetrosis (Okada et al., 1994).

Fos is also rapidly induced in stimulated T cells and contributes to T cell homeostasis and activation by the

Table 1. Overview on mouse strains with *Fos*-deletions.

Mouse strain	Affected cell type / tissue	Phenotype
Fos$^{-/-}$	Osteoclast / osteoblast / bone	Osteopetrosis Impaired osteoblast proliferation
	Mast cell / immune system	Degranulation defect
	T cell / immune system	Impaired *Tcrb* recombination
	Neuron / CNS	Abnormal behavior Impaired light-induced photoreceptor cell death Increased kainic-acid-induced cell death
	Keratinocyte / skin	Impaired skin carcinogenesis
Fos$^{\Delta CNS}$	Neuron / CNS	Impaired spatial and associative learning
Fos$^{\Delta ep}$	Keratinocyte / skin	Impaired skin carcinogenesis
Fos$^{Fosl1/Fosl1}$	Osteoclast / bone	Rescue of osteopetrosis
	Neuron / CNS	Rescue of light-induced photoreceptor cell death

The first column shows the specific mouse strains with complete or tissue specific Fos-deletions. The affected cell types and/or tissues are listed in the second column, and the third column summarizes the specific phenotypes, which have been described for the respective mouse strain. CNS: central nervous system, ep: epidermis, Fosl1: FOS-like antigen 1.

Table 2. Overview on *Fos*-transgenic mouse strains.

Mouse strain	Affected cell type / tissue	Phenotype
MT-Fos-LTR	Chondroblast / osteoblast / bone	Osteosarcoma
H2-Fos-LTR	Chondroblast / osteoblast / bone	Osteosarcoma
H2-Fos-LTR / H2-Jun-LTR	Chondroblast / osteoblast / bone	Accelerated osteosarcoma formation
H2-Fos-LTR / JunAA	Chondroblast / osteoblast / bone	Reduced osteosarcoma
H2-Fos-LTR / Rsk2$^{-/y}$	Chondroblast / osteoblast / bone	Reduced osteosarcoma
hK1-vFos	Keratinocyte / skin	Epidermal hyperplasia and squamous papillomas
bK5/A-Fos	Keratinocyte / skin	Reduced squamous tumors during chemically induced skin carcinogenesis

The fist column shows the genotype of specific mouse strains. The affected cell types and/or tissues are listed in the second column, and the third column summarizes the specific transgene-induced phenotypes. MT: inducible metallothionein promoter, H2: MHC class I H2-K^{b} promoter, LTR: polyadenylation signal from the FBJ virus, hK1: human keratin-1 promoter, bK5: bovine keratin-5 promoter.

regulation of various cytokines (Macian et al., 2000, 2001; Martins et al., 2008). However, upon T cell receptor stimulation *Fos*-deficient mice were comparable to wild-type controls with regard to peripheral T cells proliferate and cytokine production (Jain et al., 1994). Moreover, Fos is not essential for the regulation of T cell apoptosis that plays an important role in T cell development, positive and negative selection, and function (Gajate et al., 1996; Bierbaum et al., 2003). These data suggested that other Fos family members could substitute for Fos function during T cell homeostasis and activation. However, $Fos^{-/-}$ mice showed a considerable inhibition of early T cell development with significant lower thymocyte numbers compared to wild-type controls (Wang et al., 1992, 2008). This phenotype is, at least in part, due to an unexpected function of *Fos as a direct regulator of T cell antigen receptor-ß (Tcrb)* recombination by binding to an AP-1-binding site in a recombination signal sequence and physical interaction with RAG recombinases (Wang et al., 2008). It is noteworthy that the regulation of *Tcrb* recombination by Fos is independent of its usual function as a transcriptional regulator.

Fos expression is potently induced by aggregation of the surface FcεRI receptor on mast cells, suggesting a functional implication in mast cell activation and/or function (Baranes and Razin, 1991). Mast cells are tissue-localized effector cells of the innate immune response implicated in inflammatory processes and initiation of adaptive immune responses by recruiting T cells to draining lymph nodes of an infected site. Indeed, *Fos*-deficient mast cells showed a severe FcεRI-mediated degranulation defect, accompanied by altered expression of various cytokines and proteins, such as Swap70, Vamp7, and Syt1, directly involved in the degranulation process (Lee et al., 2004).

Bone development and remodeling

Bone is a dynamic organ that is characterized by continuous tissue renewal and the integrity of bone function is assured by a tightly controlled balance between bone formation and resorption facilitated by tightly adjusted action of osteoblasts and osteoclasts, repsectively (Karsenty, 2003). The expression pattern of Fos protein during mouse embryogenesis and in adult tissues indicated a possible role in bone development

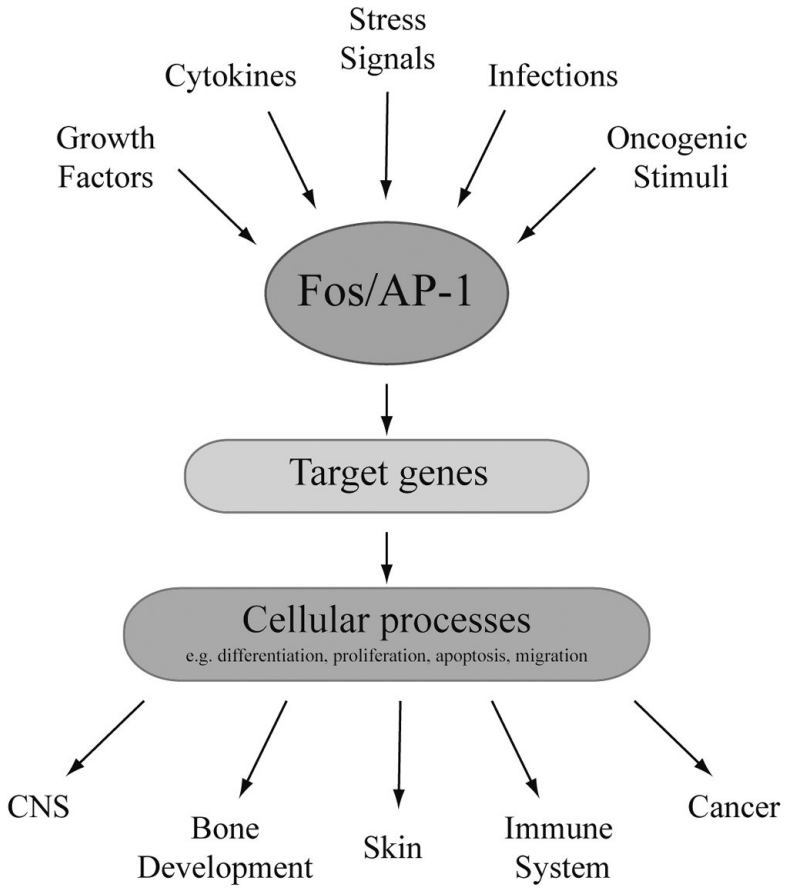

Fig. 1. The functional integration of Fos/AP-1 signaling. Numerous extra- and intracellular stimuli induce transcription and/or activity of Fos/AP-1. Upon activation Fos/AP-1 regulates the expression of downstream target genes implicated in the regulation of various cellular processes, and thereby contributes to normal physiological as well as pathological conditions, including cancer.

and remodeling. Indeed, ectopically expressed *Fos* protein in transgenic mice specifically affected the skeleton, and *Fos* knock-out mice exhibited severe osteopetrosis due to a complete lack of mature osteoclasts (Ruther et al., 1987; Johnson et al., 1992; Wang et al., 1992; Grigoriadis et al., 1994). The signal transduction pathways operating in osteoclastogenesis have been extensively studied and it turned out that Fos is at the receiving end of several signaling cascades triggered by essential growth factors such as Csf1 and Tnfsf11 (also known as M-CSF and RANKL) (Wagner and Matsuo, 2003; Wagner and Eferl, 2005). Tnfsf11 is a member of the TNF superfamily and was initially identified on activated T cells. However, it was shown subsequently that Tnfsf11 is also expressed on the surface of osteoblasts and is a key molecule in the induction of osteoclastogenesis (Takahashi et al., 1999; Wagner and Eferl, 2005). Under pathogenic conditions such as rheumatoid arthritis (RA), Tnfsf11 is secreted by a variety of synovial cells, including activated T cells, thereby promoting extensive osteoclastogenesis and bone resorption (Zenz et al., 2008). RA is considered an autoimmune disorder and is characterized by synovial inflammation, joint destruction, and excessive subchondrial bone resorption. In addition to osteoclast-mediated bone erosion the generation of pro-inflammatory cytokines and matrix metalloproteinases (MMPs) is important in the pathogenesis of RA. Thus, therapies targeting respective cytokines are highly effective but still insufficient for sustained clinical remission (Scott and Kingsley, 2006). Both pro-inflammatory cytokines and MMPs are well-known targets of Fos/AP-1, and ectopic over-expression of Fos in transgenic mice leads to MMP induction and joint destruction (Shiozawa et al., 1992; Gack et al., 1994), supporting the hypothesis that Fos is an important contributer to inflammatory bone disease and can affect the severity of RA. The essential requirement of osteoclasts and Fos expression in RA was demonstrated in transgenic mice expressing human TNFα (*hTNFtg* mice) that develop several hallmarks of RA. The breeding of *hTNFtg* mice into a *Fos*-deficient background resulted in a complete absence of osteoclasts and an efficient protection from bone erosion (Redlich et al., 2002). Moreover, administration of short double-stranded DNA oligonucleotides sharing an AP-1-binding motif or a selective small molecule inhibitor of Fos/AP-1 reduced the amount of inflammatory cytokines, as well as MMPs, and inhibited or resolved arthritis in a preclinical mouse model of the disease (Shiozawa et al., 1997; Aikawa et al., 2008).

Fosl1, which encodes the Fos family member Fra1, and the nuclear factor of activated T cells c1 (*Nfatc1*) have been identified as direct Fos target genes in osteoclasts (Takayanagi et al., 2002). Accordingly, *Fos*-dependent functions in osteoclasts can be substituted by

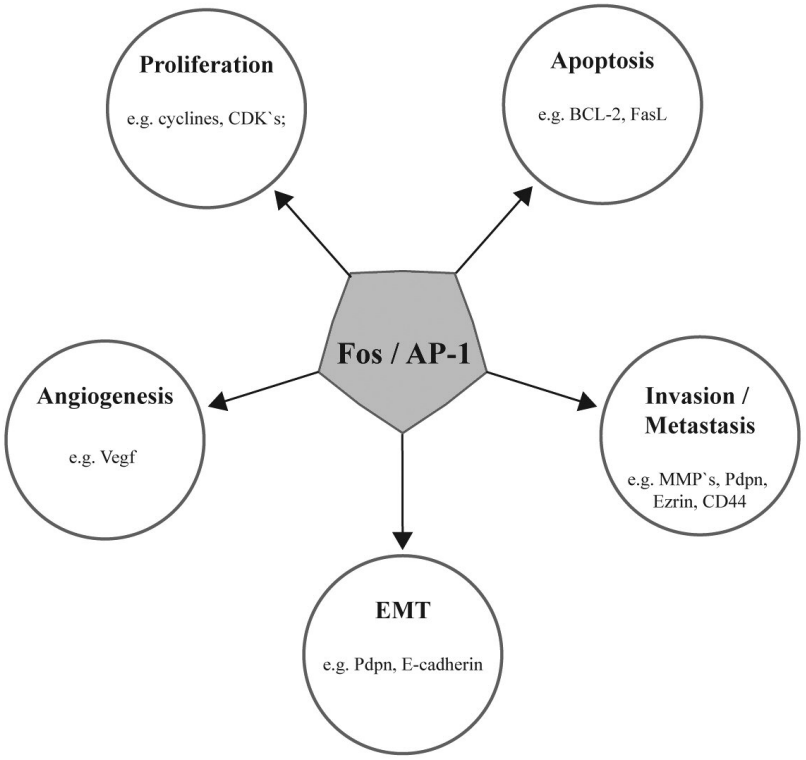

Fig. 2. Fos/AP-1 regulated processes and target genes in cancer. Fos/AP-1 is a central regulator of tumor-associated target genes during carcinogenesis and is critically involved in cellular processes, such as proliferation, apoptosis, angiogenesis, epidermal-mesenchymal-transition (EMT), invasion and metastasis.

ectopic NFAT or Fra1 expression, or in the case of replacement of the *Fos* gene locus by the *Fosl1* gene ($Fos^{Fosl1/Fosl1}$) (Fleischmann et al., 2000; Matsuo et al., 2000, 2004). Another Fos target gene, *Ifnb1*, is an antagonist of osteoclastogenesis interfering with Tnfsf11-induced expression of Fos protein in osteoclast precursors, supporting the existence of a negative feedback loop that prevents extensive osteoclastogenic activity of Fos (Takayanagi et al., 2002).

Although Fos seems to be dispensable in determining the osteoblastic lineage *in vivo*, *Fos*-deficient osteoblasts exhibited impaired growth behavior in culture, indicating that Fos is implicated in the control of osteoblast proliferation (Fu et al., 2005). The same study also unraveled an attractive model in which the hormone leptin determines the extent of bone formation by a new molecular mechanism involving sympathetic signaling, Fos/AP-1 activity, and molecular clock gene regulation.

Fos function in the central nervous system

The unique morphological and excitable properties of nerve cells endow them with specialized properties that permit the reception, transmission, and storage of information. It is well-established that trans-synaptic signals cause rapid responses in neurons occurring over a time frame ranging from milliseconds (e.g. opening of ligand-gated channels) to seconds and minutes (e.g. second messenger-mediated events). Meanwhile, we know that trans-synaptic activation also elicits slower, long-term responses in neuronal cells that are correlated with - and in most cases depend on - induction of new genetic programs.

Despite the fact that *Fos* transcription is markedly induced in neuronal cells by neurotransmitters, electric excitation and growth factors *in vitro*, and during stimulation of the intact nervous system *in vivo* (Sagar et al., 1988; Sheng and Greenberg, 1990), *Fos*-deficient mice did not exhibit an obvious defect in central nervous system (CNS) development. However, emerging evidence suggests that Fos is essential in regulating neuronal cell survival versus cell death. As an example, ablation of Fos prevented light-induced photoreceptor cell death and retinal degeneration, suggesting a pro-apoptotic function of Fos in this cell type (Hafezi et al., 1997). Similar to the situation in osteoclasts, a *Fosl1* knock-in into the *Fos* gene locus could substitute for Fos functions during light-induced apoptosis of photoreceptor cells (Fleischmann et al., 2000). Recently, two different pathways of light-induced photoreceptor cell death, depending either on transducin or AP-1 activity, were suggested, and specific genetic programs as well as gene regulatory networks were predicted, employing global gene expression analysis on samples from several knock-out mouse models (Hao et al., 2002; Krishnan et al., 2008). Yet, in contrast to the situation in photoreceptor cells, Fos turned out to be a crucial genetic regulator of neuronal excitability and survival in a mouse model of kainic-acid-induced seizures (Zhang et al., 2002b).

In addition to its role in neuronal cell survival versus cell death, Fos has been postulated to participate in the molecular mechanisms of learning and memory (Paylor et al., 1994; Tischmeyer and Grimm, 1999). Despite a strong induction of Fos expression in the hippocampus after spatial learning, mutant mice carrying a hippocampal region-specific Fos deletion, exhibited normal spatial learning behaviors in both Morris water maze and Barnes maze tests (Zhang et al., 2002). In contrast, Fleischmann and colleagues demonstrated in a mouse model with a CNS-specific Fos deletion ($Fos^{\Delta CNS}$) that mutant animals exhibited normal general and emotional behavior but were specifically impaired in hippocampus-dependent spatial and associative learning tasks (Fleischmann et al., 2003). These learning deficits were most likely due to a reduction of NMDA receptor-dependent long-term potentiation in hippocampal synapses. In a more recent study, antisense oligonucleotide microinfusion or *Fos*-deficient mice were used to demonstrate that *Fos*-mediated gene transcription in the parabranchial nucleus, amygdala, or insular cortex plays a crucial role in the acquisition and/or consolidation, but not the retrieval, of long-term taste memory (Yasoshima et al., 2006).

As immunohistochemical staining or *in situ* hybridization of brain sections have revealed a significant anatomical and temporal specificity of Fos expression in the CNS, particularly under stress conditions, Fos became the most widely used biomarker and extremely powerful tool to monitor neuronal activity *in vivo* or *ex vivo* and to reveal the connection between activated neurons within the CNS (Sheng and Greenberg, 1990; Kovacs, 2008). Meanwhile, several transgenic animal models have been established that utilize the *Fos* promoter for simple, rapid, and quantitative activity mapping in the CNS *in vivo* or to drive expression of genes of interest in activated neurons (Smeyne et al., 1992; Robertson et al., 1995; Muphy et al., 2004; Reijmers et al., 2007; Matsuo et al., 2008).

Fos function in cancer development and progression

In the past, many studies focused on the oncogenic function of Fos protein and highlighted its key role in neoplastic transformation and epithelial-to-mesenchymal transition leading to invasive growth of cancer cells and metastasis. Initially, Fos was identified as an oncoprotein in the Finkel Biskis-Jinkis osteosarcoma virus and the fact that its function was augmented by growth factors, membrane-bound and cytoplasmatic oncogenes, as well as carcinogens and tumor-promoting agents supported the idea that Fos is a potent oncogenic transcription factor (Curran et al., 1983; Van Beveren et al., 1983; Angel and Karin, 1991). In this regard, several reports demonstrated *Fos* amplification or expression in human tumor tissues, such as osteosarcomas (Gamberi et al., 1998; Papachristou et al., 2003), cervical cancer (Prusty

and Das, 2005), endometrial carcinomas (Bamberger et al., 2001), hepatocellular carcinomas (Yuen et al., 2001), ovarian cancer (Tsuda et al., 2004), and in some human cancers Fos protein levels correlated with malignant progression or poor prognosis (Volm et al., 1993; Aoyagi et al., 1998; Mahner et al., 2008).

Again, several genetically modified mice exhibiting alterations predominantly in bone and skin have shed light on the role of Fos in the context of tumor formation and malignant progression *in vivo* (Tables 1 and 2).

Bone tumors

When widely over-expressed in transgenic mice (*MT-Fos-LTR* or *H2-Fos-LTR*), ectopic Fos expression caused osteosarcoma formation by transformation of chondroblasts and osteoblasts, which identifies these two cell types as specific cellular targets of Fos-induced tumorigenesis (Ruther et al., 1989; Wang et al., 1991; Grigoriadis et al., 1993). Activation of Fos in transgenic mice and osteoblast cell lines resulted in strong up-regulation of cell cycle regulators (e.g. Cyclin D1, Cyclin A and Cyclin E), which may contribute to uncontrolled proliferation (Sunters et al., 1998, 2004). *Fos-Jun* double transgenic mice developed osteosarcomas at a higher frequency than single *Fos* transgenic animals, suggesting a cooperative effect (Wang et al., 1995). Indeed, crossing *H2-Fos-LTR* mice with animals harboring mutant *Jun* alleles that had the Jun N-terminal kinase (Jnk) phospho-acceptor serines changed to alanine (*JunAA*) revealed reduced formation of bone lesions (Behrens et al., 2000). These data confirm that the phosphorylated Jun protein is an important partner for oncogenic Fos and that the Jun/Fos heterodimeric complex regulates proliferation and cellular transformation of osteoblasts *in vivo*. It is worth noting that impaired osteosarcoma formation in *H2-Fos-LTR* mice was also observed in the absence of the growth factor-regulated S6 kinase (Rsk2), supporting that Fos-dependent transformation of bone cells requires post-translational regulation via Rsk2 signaling (David et al., 2005). Indeed, lack of Fos phosphorylation at Ser362 by Rsk2 resulted in rapid protein destabilization and has been thought to be responsible for decreased proliferation and increased apoptosis of transformed osteoblasts.

Skin tumors

Greenhalgh and colleagues generated transgenic mice that express v-Fos under the control of the human *keratin-1* promoter (*hK1-vFos*) to investigate the role of activated Fos protein in the transformation of keratinocytes *in vivo* (Greenhalgh et al., 1993b). Adult transgenic mice displayed hyperplasia and hyperkeratosis and developed benign squamous papillomas after long latency. Meanwhile, they crossed *hK1-vFos* transgenic animals with numerous genetically modified mouse strains to unravel the synergism of v-Fos with other oncogenes and/or tumor suppressor genes, such as *Ras, Tgfa, Tp53,* and *Pten*, in neoplastic transformation of epidermal keratinocytes (Greenhalgh et al., 1993; Wang et al., 1995, 2000; Yao et al., 2008). The role of Fos-containing protein complexes during multistage skin carcinogenesis was further investigated using another transgenic mouse model in which a negative Fos mutant was conditionally expressed in keratinocytes (*bK5/A-Fos*). Whereas inhibition of Fos/AP-1 activity during chemically induced skin carcinogenesis dramatically reduced the number of benign and malignant squamous lesions, expression of A-Fos after tumor formation caused squamous tumors to trans-differentiate into sebaceous adenomas (Gerdes et al., 2006). Thus Fos/AP-1 activity in keratinocytes regulates tumor cell lineages and is essential to maintain the squamous tumor cell identity. In line with these data, $Fos^{-/-}$ mice, mice expressing a transactivation negative version of the Fos partner Jun and animals that specifically lack Fos expression in keratinocytes ($Fos^{\Delta ep}$) showed reduced tumor formation in mouse models of skin carcinogenesis and revealed an essential function of Fos during late stages of tumor development (Saez et al., 1995; Young et al., 1999; Durchdewald et al., 2008).

Yet, how could Fos affect malignant progression of epithelial tumor cells? One possible answer was found by Reichmann and colleagues, who showed that over-expression of a conditional FosER fusion protein in mammary epithelial cells caused a loss of epithelial polarity and augmented invasive growth, most likely by induced epithelial-mesenchymal transition (EMT) (Reichmann et al., 1992). EMT is a critical process in tumor progression and metastasis providing tumor cells with the capability to escape from the primary tumor, to invade the surrounding tissues, and to migrate to distant regions of the body. Characteristic molecular features of EMT are loss of cell–cell adhesion and apical–basal cell polarity, as well as the increased motility of cells accompanied by nuclear translocation of ß-catenin, accelerated TGF-ß signaling, loss of epithelial markers, such as E-cadherin, and gain of mesenchymal markers, such as vimentin (Thiery and Sleeman, 2006; Jeanes et al., 2008). Indeed, all these features could be detected in epithelial cells with ectopic Fos over-expression (Eger et al., 2000, 2004; Mejlvang et al., 2007).

Fos target genes in cancer

The identification of key regulators of distinct molecular processes in cancer cells that are under the direct control of Fos is essential to understand its function during tumor development and to find additional therapeutic targets for novel strategies of translational cancer research. Despite the well-documented function of Fos in neoplastic transformation and malignant progression, only a few unambiguously identified tumor-associated target genes have been described so far. Therefore, genome-wide approaches in

informative tumour models are necessary in order to define Fos-dependent genetic programs in cancer that will most likely vary according to the tumor type and the conditions. In the past, Ozanne and colleagues performed gene expression analysis comparing control fibroblasts with v-Fos transformed fibroblasts and found many candidate genes implicated in cellular processes of cytoskeleton rearrangement, motility, and proteolysis, suggesting that Fos target genes are important effectors of cellular invasion (Scott et al., 2004; Ozanne et al., 2007). In line with this assumption, Fos-dependent gene transcription has been shown to drive invasive tumor growth in Drosophila (Uhlirova and Bohmann, 2006).

More recently, we analyzed skin tumor samples from control and $Fos^{\Delta ep}$ mice that developed due to ectopic expression of a constitutive active mutant of human son of sevenless (SOS-F), a potent upstream activator of oncogenic Ras, in keratinocytes (Sibilia et al., 2000). Genome-wide gene expression analysis revealed a comprehensive list of 372 differentially expressed genes that significantly discriminate skin tumors from *SOS-F/*Fos^{floxed} and *SOS-F/*$Fos^{\Delta ep}$ animals (Durchdewald et al., 2008). Numerous genes of this list were previously identified as tumor-associated candidates in mouse models of skin carcinogenesis, and gene clustering according to their functional annotation showed that most of them are implicated in distinct tumorigenic features, such as cellular movement and morphology, cell cycle control, cell death and cell signaling (Hummerich et al., 2006; Durchdewald et al., 2008). Interestingly, one candidate gene whose expression critically depends on Fos activity encoded the small mucin-like glycoprotein podoplanin (Pdpn). Pdpn has attracted great interest in the field of cancer research since its expression correlated with malignant progression and metastasis, and could promote tumor cell invasion *in vitro* and *in vivo* by EMT-dependent and -independent mechanisms (Wicki et al., 2006, Wicki and Christofori, 2007).

Conclusion and Outlook

In conclusion, a large body of experimental evidence clearly demonstrates a unique role of the transcription factor Fos in normal tissue development and homeostasis, and that deregulation of Fos activity critically contributes to pathophysiological processes, including cancer. However, genome-wide approaches and detailed analysis of Fos-dependent genetic programs will be essential to comprehensively understand the causal connectivity between altered Fos activity and distinct human disorders.

There is a controversial discussion on the question whether transcription factors themselves, such as Fos, could serve as suitable drug targets for clinical application. Some general doubts are that (i) Fos is ubiquitously expressed and critical for numerous important cellular processes, (ii) Fos is a member of a larger protein family showing putative redundant functions under pathophysiological conditions and/or in transformed cells, and (iii) frequent mutations in the *Fos* coding region have not been identified so far that could serve as putative target site for drug interference. However, using three-dimensional pharmacophore modeling Aikawa and colleagues succeeded in *de novo* design of a specific small-molecule inhibitor for Fos/AP-1 that resolved arthritis in a preclinical mouse model (Aikawa et al., 2008). Although additional clinical studies are required to determine its therapeutic efficacy, this inhibitor might also be suitable for other clinical applications, including cancer therapy. Yet, in contrast to the classical concept of Fos as an oncogenic transcription factor, a more recent study in *Trp53/Fos* double knockout mice that developed highly proliferative and invasive rhabdomyosarcomas has raised the idea that it also has tumor-suppressive functions in specific cancer cells, and caution against the therapeutic use of Fos inhibitors in some human cancers (Eferl and Wagner, 2003; Fleischmann et al., 2003). Furthermore, Fos expression levels in tissue samples of human non-small cell lung cancer and thyroid carcinoma were significantly lower compared to normal tissue (Levin et al., 1995; Liu et al., 1999), and loss of Fos expression in human gastric and ovarian carcinomas correlated with disease progression and was independently associated with unfavorable progression-free as well as overall survival (Welsh et al., 2001; Meinhold-Heerlein et al., 2005; Jin et al., 2007; Mahner et al., 2008).

Despite the fact that Fos was identified more than two decades ago, it still maintains a lot of its mystery. However, the availability of a large variety of defined mouse models and indicative downstream target genes is a promising starting point for novel drug development and drug assessment in the near future.

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