Hypothesis

c-Fos transrepression revisited

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Abstract The c-*fos* proto-oncogene was discovered by homology to transforming viral genes, leading to speculation that transforming viruses had captured a cellular gene involved in cell cycle control. Indeed overexpression of c-Fos protein led to deregulated growth control, and c-Fos was thought to be so critically involved in cell cycle control that transcriptional transrepression of its own promoter was interpreted as a negative feedback mechanism. However, recent findings render this conclusion improbable, Fos transrepression being most parsimoniously explained as transcriptional squelching imposed by artificially elevated levels of exogenous Fos protein.

Key words: Transcription regulation; Transcription factor; Transcription coactivator; Fos; AP-1

The gene encoding c-Fos protein, a component of the AP-1 transcription factor, is induced rapidly and transiently, characterised by pronounced post-inductional transcriptional attenuation (reviewed in [1]). When exogenous c-Fos is overexpressed the c-*fos* gene is also transcriptionally repressed. This transrepression involves the c-*fos* promoter serum response element (SRE), and the C-terminal domain of c-Fos (absent from viral v-Fos) [2–10], which requires serine phosphorylation [8,11]. After stimulating v-Fos overexpression from a c-*fos* promoter in transient transfections, there is induction but no post-inductional attenuation of either the exogenous or endogenous c-*fos* promoters, and this phenotype is dominant when v-Fos and c-Fos are exogenously coexpressed [3].

The above observations led to the concept that c-Fos regulates post-inductional transcriptional attenuation of its own gene. However, an accumulation of circumstantial evidence from different laboratories during the last 2 years make this seem unlikely. Transcription from a mutant c-*fos* allele, with an intact promoter driving the transcription of an mRNA encoding a disrupted protein, was induced and down-regulated normally in ES cells and 3T3-like fibrobalsts lacking c-Fos protein [12], demonstrating that c-Fos is unnecessary for post-inductional transcriptional attenuation in these cells. However, other molecules may have compensated for this function, such as the related Fra-1 protein which transrepresses similarly to c-Fos [6], and was present in these cells [12]. In other work, transcription from the c-*fos* promoter was found to correlate with the activity of inducible kinases targeting the SRE [13]. Their activity is in turn attenuated by phosphatases (see references in [14]), without apparent involvement of c-Fos or Fra-1 proteins, although this cannot be excluded.

An alternative explanation for c-Fos transrepression is squelching (Fig. 1), where the c-Fos C-terminal domain would sequester a limiting coactivator required for SRE-dependent transcription [15]. Several recent developments support this concept. For instance, steroid receptors require the transcriptional coactivator CREB binding protein (CBP) to activate target genes [16–18] (reviewed in [19]). Inhibition of AP-1 activity by steroid receptors is caused by receptors sequestering limiting amounts of CBP required by AP-1 [17]. The c-Fos transrepressing C-terminal domain also interacts with CBP [20], as do the c-*fos* SRE-transactivating ternary complex factors (TCF) Sap-1a and Elk-1 [21,22]. Whereas expression of high amounts of exogenous c-Fos inhibited transactivation [23,24], probably by sequestering limiting amounts of CBP in the cell (see [19]), the c-Fos C-terminus could activate transcription from a GAL4 binding site when expressed at low concentrations and fused to an autonomous GAL4 DNA binding domain [20]. Taking these observations together, the most likely explanation for c-Fos transrepression of its own promoter is transcriptional squelching of the c-*fos* SRE following transient transfection (Fig. 1). Exogenously overexpressed c-Fos would sequester CBP or other coactivators away from the c-*fos* promoter [15], possibly including TFIIF-mediated transactivation of the SRE [25–27]. Although squelching could potentially contribute to some promoter down-modulation after induction of endogenous c-Fos, this seems unlikely as judged by the normal post-inductional repression of cells lacking c-Fos [12].

The dominant phenotype of v-Fos over transrepression referred to above needs to be reconciled with this model. Those observations were made in studies employing synthetic promoter constructs [3] which unintentionally all contained an AP-1-like site in the c-*fos* promoter [28]. The fact that v-Fos expression led to sustained c-*fos* transcription could therefore be due to v-Fos directly binding and transactivating an AP-1 site in the c-*fos* or another promoter, which would be mechanistically distinct from c-Fos transrepression caused by squelching. If so, v-Fos could be dominant over c-Fos since CBP availability would not affect the activating function of v-Fos, which lacks the amino acids required for interaction with CBP [20]. This explanation provides an experimentally testable paradigm. The dominant phenotype of v-Fos should require the DNA binding function, unlike transrepression by c-Fos.

Although aberrant Fos levels influence cell transformation, there is no compelling evidence that normally regulated c-Fos plays any direct role in cell-cycle control [14,29]. Intriguingly, unregulated Fos expression perturbs growth control in a man-

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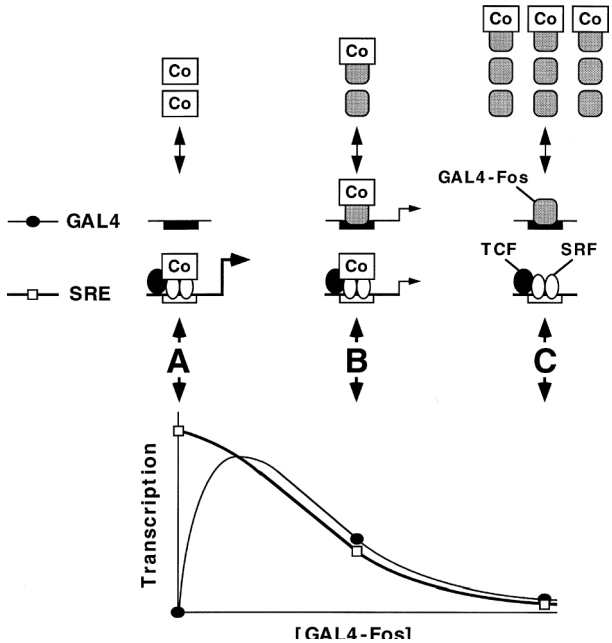

Fig. 1. SRE-transrepression by the c-Fos C-terminal domain, here represented as a fusion protein with the DNA-binding domain of GAL4 (GAL4-Fos [20]), by squelching. Transcriptional activity of GAL4 or SRE promoter elements are depicted as a function of GAL4-Fos concentration in cartoon form above, and as dose–response curves below. A: In the absence of GAL4-Fos, GAL4-dependent promoters are silent and SRE activity is determined by coactivator availability (Co) to SRE-bound transcription factors SRF and TCF. B: In the presence of GAL4-Fos, competition for coactivator causes some squelching of SREs. However, coactivator recruitment to GAL4 sites causes activation relative to 'A'. C: Upon expression of GAL4-Fos in large stoichiometric excess, coactivator is sequestered away from all promoters, severely squelching transcription. Since cellular levels of coactivator can be limiting, squelching can panoramically regulate the activity of diverse genes via coactivator competition between promoters analogously to 'B' and 'C' above, relative transcriptional activity being dependent on affinity for coactivators (for references and more details see [15,19,22]).

ner dependent on the duration of expression, but not the stage of the cell cycle where Fos expression begins [29]. Therefore the concept that c-*fos* is a regulator of the cell cycle which orchestrates its own repression by negative feedback has not been strengthened by recent findings.

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