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# Biological function of the USF family of transcription factors

**Review Article**

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## Summary

**USF is a family of ubiquitous transcription factors that are structurally related to the Myc oncoproteins and also share with Myc a common DNA-binding specificity. While the structure and DNA-binding properties of the USF transcription factors are well characterized, their biological function is only beginning to emerge. Experiments in cultured cells suggest that USF can antagonize the activity of Myc in cellular proliferation and transformation. The phenotype of USF-deficient mice indicates an additional and essential role of USF in embryonic development as well as pleiotropic functions in adult animals.**

## I. Introduction

Although USF was one of the first gene-specific transcription factors to be identified in eukaryotes, its biological function has, until recently, remained quite elusive. For this type of transcription factor, biological function can be revealed by the relationships linking their various target genes. However, many other transcription factors, including all the members of the TFE3 and Myc families, recognize the same DNA-binding sites as USF (Beckmann *et al.*, 1990; Fisher *et al.*, 1991; Blackwood and Eisenman, 1991; Ayer *et al.*, 1993). This redundancy greatly complicates the identification of genes that are regulated by USF. Consequently, and despite the development of dominant negative mutants of USF (Meier *et al.*, 1996; Krylov *et al.*, 1997), few cellular genes can be unambiguously classified as *bona fide* USF targets. Nevertheless, recent studies, summarized here, are beginning to shed light on the biological function of this important family of transcriptional regulators and its essential role in embryonic development and growth control.

## II. The USF family of transcription factors

The USF proteins were first identified through *in vitro* transcription studies as an activity that stimulated expression of the adenovirus major late promoter (Sawadogo and Roeder, 1985; Carthew *et al.*, 1985, Miyamoto *et al.*, 1985). Purification of USF to homogeneity from HeLa cell nuclear extracts indicated that this transcription factor was composed of two different polypeptides with molecular masses of 43- and 44-kDa (Sawadogo *et al.*, 1988). Cloning of the corresponding genes, respectively called *Usf1* and *Usf2*, revealed that the USF proteins belong to the same basic-helix-loop-helix-leucine zipper (bHLH-zip) group of transcriptional regulators as the Myc oncoproteins (Murre *et al.*, 1989; Gregor *et al.*, 1990; Sirito *et al.*, 1992).

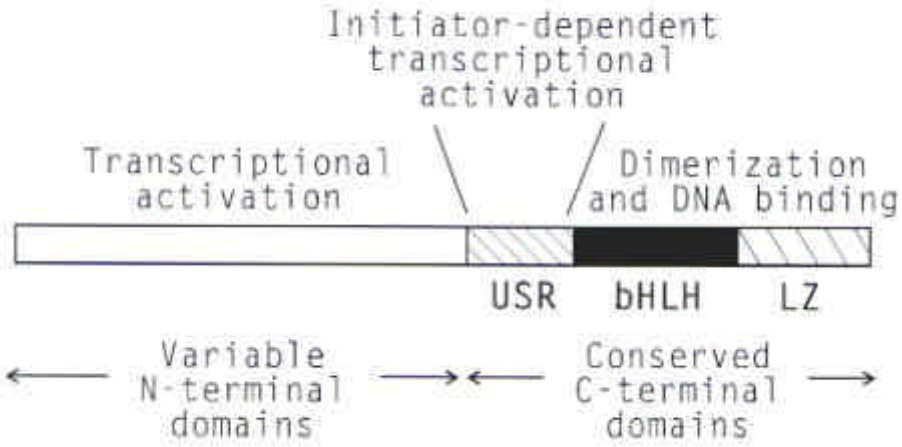


**Figure 1** General structure of the USF proteins. Locations of the USF-specific region (USR), basic-helix-loop-helix (bHLH) domain and leucine zipper (LZ) are shown. The role and evolutionary conservation of the different USF domains are also indicated.

USF cDNA clones have now been isolated from several other species, including mouse, *Xenopus*, and sea urchin (Kozlowski *et al.*, 1991; Kaulen *et al.*, 1991; Sirito *et al.*, 1994). Amino acid comparisons have revealed a strong evolutionary conservation of the bHLH domain needed for dimerization and DNA binding (**Figure 1**).

The C-terminal leucine zipper is also conserved in vertebrate USFs, where it plays an important role in dimerization specificity. Also extremely conserved in all USF family members is a small domain, located just upstream of the basic region, that has no homologies in other bHLH transcription factors (**Figure 1**). This USF-specific region or USR is necessary and sufficient for transcriptional activation by USF of promoters containing both a TATA box and an initiator element. The USR also contains an atypical nuclear localization signal that can function independently of a second nuclear localization signal present in the basic region (Luo and Sawadogo, 1996b).

Outside of the USR and bHLH-zip domains, the sequences of USF1 and USF2 diverge considerably, suggesting that the two proteins can establish different interactions with other transcription factors and thus regulate different sets of genes. Interestingly, the regions of the *Usf1* and *Usf2* genes that are highly homologous in human and mouse extend outside of the coding region to also include the 5' and 3' untranslated regions of the mRNAs (Sirito *et al.*, 1994; Henrion *et al.*, 1996). This unusual feature indicates that the expression of the *Usf* genes is controlled by posttranscriptional mechanisms (e.g., translational regulation or message stability) that are conserved between species and involve untranslated regions of the mRNAs (Duret *et al.*, 1993). The genomic structure of both *Usf* genes is characterized by multiple exons, many of which correspond precisely to discrete functional domains of the transcription factors (Lin *et al.*, 1994, Henrion *et al.*, 1996).

The USF1 and USF2 polypeptides are both ubiquitously expressed and the USF1·USF2 heterodimers represent the major USF species in most tissues and cell types. USF1 homodimers are expressed at lower concentration, while the USF2 homodimers are usually scarce, except in B cell lines (Sirito *et al.*, 1994; Viollet *et al.*, 1996). The existence of differentially spliced USF messages has been reported for both the *Usf*1 and *Usf*2 genes, but the contribution of minor isoforms to the biological function of USF remains unclear (Gregor *et al.*, 1990; Sirito *et al.*, 1994; Viollet *et al.*, 1996).

## III. Dimerization and DNA binding properties of USF

The USF proteins exist in solution and also bind DNA as dimers. Efficient dimerization requires both the bHLH domain and the adjacent leucine zipper (Beckmann and Kadesh, 1991; Sirito *et al.*, 1992). By stabilizing the interaction between subunits, the leucine zipper of USF controls the specificity of dimerization and prevents dimerization with other bHLH proteins. Consequently, the USF proteins are excluded from the class of bHLH transcription factors whose activity can be regulated by formation of DNA binding-deficient dimers with members of the Id family of proteins (Sun *et al.*, 1991).

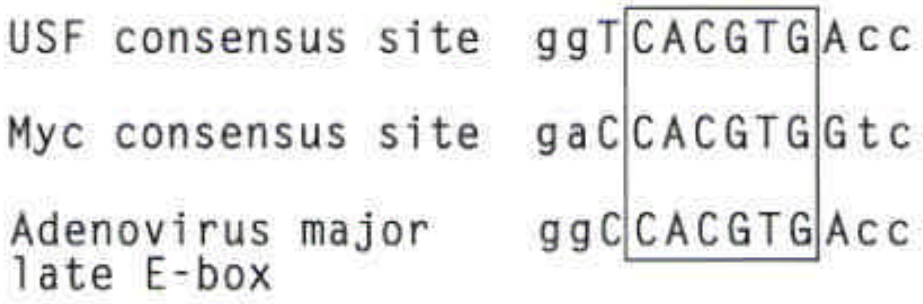


**Figure 2**: USF and Myc have very similar DNA-binding specificities. Shown are the complete consensus sequences determined for the two transcription factors, with the most important residues in capital letters and the common core motif boxed. Also shown is the sequence of the adenovirus major late E box that is known to bind both transcription factors *in vitro* as well as *in vivo* (Li *et al.*, 1994).

The structure of the dimeric bHLH domain of USF1 in a cocrystal with DNA has been solved. Like that of Max, the DNA-binding partner of Myc, the USF bHLH is characterized by a parallel, left-handed four-helix bundle, with the basic regions contacting the DNA in the major groove (Ferré-D'Amaré *et al.*, 1994). However, the structure of USF may be quite different in solution. Indeed, there are strong indications that major conformational changes are required for a stable interaction of USF with the DNA. For example, the basic region undergoes a random coil to alpha-helix folding transition upon specific DNA recognition (Fisher *et al.*, 1993; Ferré-D'Amaré *et al.*, 1994). The presence of the leucine zipper greatly stabilizes the conformation of USF dimers (Bresnick and Felsenfeld, 1994; Lu and Sawadogo, 1994). Therefore, protein-protein interactions that would either favor or hinder essential conformational changes in the USF proteins may well contribute to the regulation of USF function. The formation of tetrameric USF species have also been implicated in the ability of the transcription factor to simultaneously interact with two DNA-binding sites (Sawadogo, 1988; Sha *et al.*, 1995).

USF1 and USF2 display identical dimerization and DNA binding specificities. Like the Myc and TFE3 family members, all USF dimers recognize palindromic E boxes characterized by a central CACGTG or CACATG sequence (Blackwell *et al.*, 1990; Kerkhoff *et al.*, 1991; Halazonetis and Kandil, 1991; Bendall and Molloy, 1994). Outside the core sequence, there are differences in the USF and Myc consensus binding sites (**Figure 2**). Most notably, T and A residues on each side of the CACGTG core sequence are essential for high USF binding affinity (M. N. Szentirmay, unpublished observation), while Myc prefers G and C residues at these locations. Nevertheless, a number of sequences, including the E boxes present in the adenovirus major late and p53 promoters, can bind either USF or Myc (Li *et al.*, 1994; Reisman and Rotter, 1993; Roy *et al.*, 1994). Together, these observations suggest that the two families of transcription factors may have both specific and common target genes.

## IV. Antagonism between USF and Myc in cellular transformation

The important role of the Myc proteins, and in particular the ubiquitous c-Myc, in promoting cellular proliferation and preventing differentiation is well documented. Furthermore, overexpression of c-Myc, whether due to gene amplification or translocation or to increased message stability, is an important parameter in cancer progression (reviewed in Marcu *et al.*, 1992; Koskinen and Alitalo, 1993). The transforming ability of c-Myc is best exemplified by its ability to elicit the complete transformation of primary cells when cotransfected with a second oncoprotein such as activated Ras (Land *et al.*, 1983). The effect of the USF proteins on cellular transformation was also investigated by focus formation assay in primary embryonic fibroblasts and is summarized in **Table 1**.

| Cotransfected expression vectors | Cellular transformation |
|---|---|
| Ras alone | No |
| Ras + c-Myc | Yes |
| Ras + USF | No |
| Ras + c-Myc + USF | No |

**Table 1**: Effect of USF and c-Myc on cellular transformation as monitored by focus formation assay in primary embryo fibroblasts.

| Deleted gene | USF1 expression | USF2 expression | Total USF level | Phenotype |
|---|---|---|---|---|
| *Usf1* | None | Increased | Unchanged | Mild |
| *Usf2* | Decreased | None | Decreased | Growth defect |
| *Usf1 + USF2* | None | None | (None) | Embryonic lethal |

**Table 2.** Phenotype of USF-deficient mice.

Cotransfection of either USF1 or USF2 with Ras did not result in the appearance of foci of morphologically transformed cells, demonstrating that the function of USF in transformation was clearly different from that of c-Myc. Instead, cotransfection of USF was found to abolish cellular transformation mediated by c-Myc and activated Ras (Luo and Sawadogo, 1996a). This inhibition of cellular transformation by USF requires not only its DNA-binding domain but also domains involved in transcriptional activation, indicating that the effect is not a simple DNA-binding competition with Myc. Rather, it seems that the activity of USF can antagonize the transforming ability of Myc. The inhibitory activity of USF1 in the focus formation assay was specific to the Myc pathway since USF1 overexpression had no effect on the cellular transformation of embryonic fibroblasts mediated by E1A and Ras. In contrast, USF2 overexpression inhibited focus formation mediated by a variety of oncogenes. However, it is unclear whether this strong antiproliferative effect of USF2 affects in all cases transformation *per se*, or whether it simply prevents the subsequent proliferation of the transformed cells (Luo and Sawadogo, 1996a).

## V. Involvement of USF in the control of cellular proliferation

Many independent observations are consistent with a role of USF in the control of cellular proliferation. First, the expression levels and the transcriptional activities of the USF proteins are both tightly regulated during the cell cycle (T. Lu and M. Sawadogo, unpublished observation) and the activity of USF is induced in response to mitogens (Zhang *et al.*, 1998; Berger *et al.*, 1998). Second, ectopic expression of USF in general, and USF2 in particular, causes strong growth inhibition in certain transformed cell lines (Luo and Sawadogo, 1996a; Aperlo *et al.*, 1996). Third, a number of cancer cell lines contain USF proteins that are active in DNA binding but completely inactive in transcription activation (Y. Qyang, X. Luo, P.M. Ismail, T. Lu and M. Sawadogo, unpublished observations). This loss of USF function, just like Myc overexpression, may well play an important role in triggering the rapid and uncontrolled proliferation of cancer cells.

Direct interactions between USF proteins and other cell cycle regulators of the basic-leucine zipper family have also been reported (Blanar and Rutter, 1992; Pognonec *et al.*, 1997). Such interactions are likely to contribute to the regulation of USF function. Finally, it is interesting to note that many of the suspected targets of USF, including the genes encoding p53, cyclin B1, and transforming growth factor-β2, are themselves involved in proliferation or cell cycle control (Reisman and Rotter, 1993; Cogswell *et al.*, 1995; Scholtz *et al.*, 1996)

## VI. Early lessons from the USF knockout mice

Mutant mice lacking either USF1 or USF2 have been constructed by individually targeting the *Usf1* and *Usf2* genes by homologous recombination in embryonic stem cells. These experiments have yielded essential information regarding the role of the USF proteins in both embryos and adult animals (Vallet *et al.*, 1997; Sirito *et al.*, 1998; Vallet *et al.*, 1998).

When analyzing the phenotype of the USF-deficient mice, it is important to remember that the major USF species normally present in most tissues and cell types is the USF1·USF2 heterodimer. Thus, phenotypic traits common to the USF1 and USF2 mutants may be caused by the absence of the heterodimers. Similarly, specific phenotypic traits in the single mutants could result either from the absence of the corresponding homodimer or the resulting increase in the other homodimer. Finally, genes that seem unaffected by either mutation may still be controlled by USF if there is a significant overlap between the functions of USF1 and USF2.

Major findings reported so far with the single and double USF1/USF2 mutants are summarized in **Table 2**. A very interesting result was the nature of the crosstalk between the *Usf1* and *Usf2* genes. Analysis in embryonic fibroblasts demonstrated the existence in USF1-null cells of a compensatory increase in USF2 expression. In sharp contrast, USF2-null fibroblasts exhibited strongly decreased USF1 expression (Sirito *et al.*, 1998). This asymmetrical cross-regulation indicates that one of the roles of USF1 may be to prevent overexpression of the

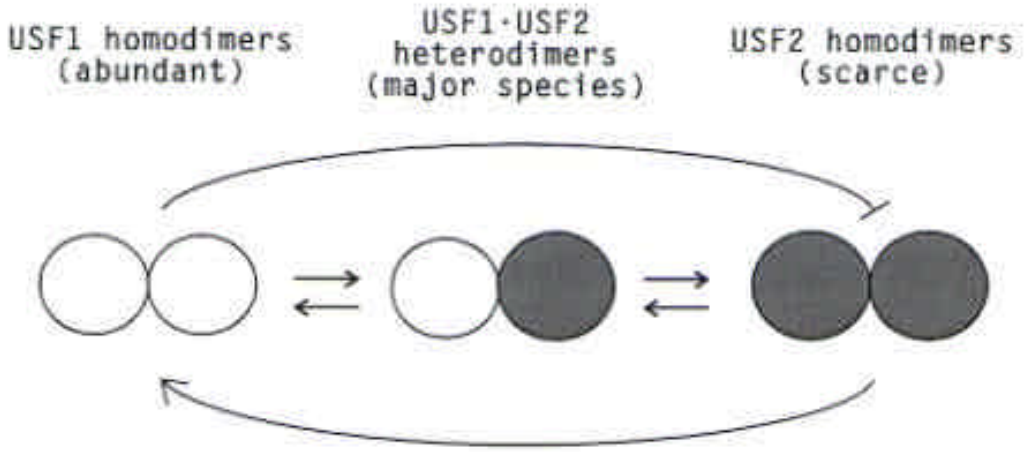


**Figure 3**: Abundance of the various USF dimers in wild-type cells. Asymmetrical cross-regulation between the two *Usf* genes explains the relatively low level of USF2 homodimers observed in most cell types

more potent USF2 protein. Note that this feedback mechanism accounts perfectly for the low concentration of USF2 homodimers present in wild-type cells (**Figure 3**).

The fact that the USF1-null mice appear normal is perfectly understandable if the increased USF2 expression can, for the most part, compensate for the absence of the heterodimers and USF1 homodimers. These animals were found to be both viable and fertile and display only mild behavioral abnormalities (Sirito *et al.*, 1998). In contrast, the USF2-null mice, where the total USF activity is greatly diminished, display a much stronger phenotype, including an obvious growth defect during embryonic development. At birth, these animals are 20-40% smaller than their wild-type or heterozygous littermates and many of them die in the first few hours. Those that survive subsequently develop in an apparently normal fashion, but remain proportional dwarfs. They also demonstrate other abnormalities, including metabolic defects and male infertility (Vallet *et al.*, 1997; Sirito *et al.*, 1998). The double USF1/USF2 mutants, as well as the mutants containing a single *Usf1* allele, are embryonic lethal (Sirito *et al.*, 1998; Vallet *et al.*, 1998). Taken together, these results demonstrate an overlapping and essential role of the USF proteins in embryonic development and pleiotropic functions in adult animals.

One common feature observed in USF-deficient mice of various genotypes is their propensity to spontaneous epileptic seizures (Sirito *et al.*, 1998 and unpublished observations). In mice, overexpression of c-Myc in oligodendrocytes causes severe neurological disturbances (Jensen *et al.*, 1998). It is therefore tempting to link these related observations in whole animals to the antagonism demonstrated by USF and Myc functions in cultured cells.

## VII. Conclusion

Analysis of the biological role of the USF proteins is complicated by the existence of two genes with partially overlapping functions. However, these ubiquitous transcription factors are clearly essential and their involvement in growth control has now been demonstrated both at the cellular and whole organism levels. A more complete understanding of the downstream targets of USF will be necessary to further delineate the importance of the different USF species in various developmental and regulatory pathways. Hopefully, the availability of the different USF-deficient mice will soon allow unambiguous determination of genes that are specific targets of either USF1, USF2, or both. By providing tissues and cell lines with different levels of USF1 and USF2 expression, these animals should also prove useful in defining the role of USF in cellular proliferation and differentiation.

The antagonism between the cellular functions of the USF transcription factors and of the c-Myc oncoprotein may lead to a better understanding of cancer progression. In particular, the loss of USF transcriptional activity in several cancer cell lines suggests the existence of a cofactor that regulates both USF1 and USF2. Thus, complete loss of USF function can be brought about by the inactivation of a single gene and this event may play a similar role as the overexpression of c-Myc in triggering uncontrolled cellular proliferation.

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