Transcription 3:4, 187-192; July/August 2012; © 2012 Landes Bioscience

Role of host cell factor-1 in cell cycle regulation

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Host cell factor-1(HCF-1) was first discovered as a cellular cofactor in the VP16-induced complex, a multi-protein DNA complex that forms on immediate early gene promoters of herpes simplex virus (HSV) to activate viral gene transcription. Subsequent research has revealed HCF-1 to be an abundant chromatin-associated protein that regulates various stages of the cell cycle. Recent reports show that HCF-1 interacts with diverse E2F proteins to induce cell cycle-specific transcription. HCF-1 can act as a scaffold to a variety of histone-modifying proteins and these HCF-1—E2F-containing multi-protein complexes can bring about context-dependent activation or repression of transcription. In this review we examine the diversity of HCF-1—E2F interactions and the variety of multi-protein complexes it occurs in, to influence the local chromatin landscape at the E2F-promoters.

Keywords: transcription, histone modification, H3K4 HMT, HCF-1, E2F

Submitted: 04/02/12

Revised: 05/09/12

Accepted: 05/10/12

http://dx.doi.org/10.4161/trns.20711

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Introduction

Since its discovery as a Herpes Simplex virus host cell factor of unknown cellular functions more than two decades ago, Host cell factor-1, or HCF-1, has emerged as an important regulator of multiple steps in the cell cycle progression. Recent studies implicate HCF-1 as a key regulatory protein in many important and diverse pathways like embryonic stem cell pluripotency, stress responses and development.[1-4] Importantly, the discovery that gene-encoding HCF-1 is over-expressed in tumors, and this over-expression is a marker that predicts poor prognosis in cancer treatment proves that the functions of HCF-1 are more complex than previously appreciated.[5]

In regulation of cell cycle, one of the well-studied roles of HCF-1, it acts as a cofactor to various members of the E2F proteins. The E2F family is one of the best-studied networks of transcriptional regulators. They regulate human cell proliferation by repressing and activating the transcription of genes required for cell cycle progression, particularly the S phase. In this review we will focus on how HCF-1 is intimately linked with transcriptional regulation of E2F-responsive promoters and discuss how HCF-1 is central to assembly of different chromatin-modifying protein complexes on these promoters.

Two Subunits of HCF-1 Regulate the Cell Cycle

HCF-1 is a heterodimeric complex of two subunits—namely N ($HCF\text{-}1_N$) and C ($HCF\text{-}1_C$) subunits. These subunits arise from the proteolytic cleavage of the 2035 amino acid precursor protein.[6,7] Although HCF-1 does not bind to DNA directly, both N and C subunits can associate with DNA. In N-terminal subunit, the Kelch domain (so named because of its similarity to drosophila protein Kelch) recognizes and associates with a short tetrapeptide HCF-1-binding motif (HBM) present in many sequence-specific DNA-binding factors like VP16. A single point mutation in the Kelch domain (called P134S) causes a temperature-induced cell-proliferation arrest and cytokinesis defect, while disrupting HCF-1 chromatin association in the temperature-sensitive baby hamster kidney cell line tsBN67.[8,9] siRNA experiments have subsequently revealed that these cell cycle defects can be segregated into two subunits where the N subunit is

required for G1 phase progression while the C subunit effects proper cytokinesis and M phase progression.[10]

HCF-1 Associates with Different Chromatin Modifiers

HCF-1 cannot bind directly to the DNA but is known to have domains that bind to many chromatin-binding proteins. Indeed, HCF-1 has been shown to interact with a number of proteins. These include transcription factors (LZIP/Luman, Zhangfei, HPIP, Sp1, GABP, YY1, FOXO3 and members of THAP zinc finger protein family), protein phosphatase PP1, cell-death protein PDCD2, deubiquitinating enzyme BAP1, and O-GlcNAc transferase (OGT).[6,11-16] Besides these interactions, HCF-1 has also been found to occur in many different multi-protein complexes. First such proteomic analysis revealed, among other proteins, an interaction with Sin3 histone deacetylase (HDAC) complex, and a previously uncharacterized human trithorax-related Set1 histone H3 lysine 4 methyltransferase (H3K4 HMT) complex.[16] Subsequently, HCF-1 has been found associated with related mixed lineage leukemia (MLL) H3K4 HMT complex and the MOF histone acetyltransferase (HAT) complex and other unrelated chromatin remodeler proteins like histone demethylase PHF8, histone deacetylase SIRT1 and histone chaperone Asf1b.[2,17-20] Double immunoprecipitation experiments have shown that HCF-1 can bind to the Sin3 HDAC and Set1 H3K4 HMT complex simultaneously, even though these complexes are associated with opposite transcriptional outcomes: repression and activation respectively.[16] However, HCF-1 associates with only Set1 H3K4 HMT but not Sin3 HDAC when bound to viral transcriptional activator VP16. These results have suggested that HCF-1 can selectively modulate chromatin structure to broadly regulate transcription.

Regulating the Cell Cycle

HCF-1 may be involved in the regulation of cell cycle at different levels. For instance, HCF-1 may directly interact with proteins involved in cell cycle (e.g., PP1). Or it may regulate the transcription of proteins that regulate the cell cycle (e.g., Pr-Set7/SETD8).[21] However, till date the most diverse and most abundant interactions of HCF-1 are with the E2F family, where it interacts with not only different members of the E2F family but also with proteins associated intimately with them.

Interactions with E2Fs. The G1 to S phase transition in mammalian cells is largely achieved by E2F transcriptional factors, which not only regulate the expression of cyclins and genes involved in DNA synthesis but also mitosis, DNA damage and apoptosis pathways. Recent studies show how HCF-1 acts in concert with E2F1 to activate transcription of S phase genes and places HCF-1 right at the heart of cell cycle transcriptional regulation.[22, 23]

The E2F protein family has currently eight members, called E2F1–E2F8. Of these, E2F1–E2F5 represent a subfamily that shares the property of binding one or more members of the pRb family, namely pRb, p107 and p130. The activation or repression specificity of E2F factors is largely conferred by the E2F-protein subunit. Among the E2F1–E2F5 proteins, E2F1, E2F2 and E2F3a primarily activate transcription ("activator E2Fs"), and E2F3b, E2F4, and E2F5 primarily repress transcription ("repressor E2Fs").

Using a number of techniques, Tyagi et al. demonstrated that HCF-1 associates with both kinds of E2Fs, namely activator (i.e., E2F1 and E2F3a) and repressor (i.e., E2F4) E2F proteins in multi-protein complexes.[23] Association of HCF-1 with both activator as well as repressor E2Fs gave the first indication that HCF-1 may have a broad role in regulation of genes throughout the cell cycle and that the associations of HCF-1 with different E2F proteins may be cell cycle dependent.[23, 24] Indeed, the HCF-1-E2F interactions are dynamic and cell cycle selective. Thus, in the early G1-phase, when the E2F-responsive promoters are repressed by E2F4 proteins, HCF-1 associates with this repressor protein. The E2F4-HCF-1 complex transitions to the activator E2F1-HCF-1 complex during the G1/S phase progression. E2F4 represses transcription by associating with pocket proteins and recruitment of a Sin3 HDAC co-repressor complex in resting and early G1 phase cells.[25] Interestingly, the E2F4-containing HCF-1 complex in early G1 phase contains the Sin3A co-repressor protein, but no pocket protein (see **Fig. 1A**). These results support the idea that E2F4 can regulate genes independently of pocket proteins by recruiting proteins like HCF-1.

During the G1 to S phase transition, when the cell prepares for active S-phase gene expression, a different HCF-1 complex binds to E2F-responsive promoters. Not only does HCF-1 associate with activator E2F1 but double immunoprecipitation experiments revealed that the E2F1-containing HCF-1 complex selectively associate with H3K4 HMT activator (and not Sin3A repressor complex). The authors proposed that HCF-1 might activate transcription of E2F-responsive promoters by recruiting MLL and Set1 complex to these promoters (**Fig. 1C**). In support of this model, experiments in which HCF-1 was depleted using siRNA did not affect promoter-binding property of E2F1 protein, but drastically diminished transcription and the presence HMTs and H3K4 trimethylation on these promoters. Thus, E2F1 affects G1 to S phase activation of E2F-responsive promoters in concert with HCF-1 and its associated HMT complexes.[23]

The HCF-1 and E2F interactions may not be as straightforward as they appear here because HCF-1 also interacts with E2F3, an E2F, which exists in two forms (with two different functions)—E2F3a, the longer isoform, acts as an activator while E2F3b, the shorter isoform, acts as a repressor. Unlike E2F1 and E2F4, E2F3 does not possess a canonical HBM. However, a non-canonical E2F3 HBM was sufficient to interact with HCF-1. Even more intriguing is the fact that both E2F3a and E2F3b possess this non-canonical HBM. It will be interesting to find out the nature of HCF-1 interactions with both forms of E2F3 and how these interactions influence the cell cycle.

Interactions with pRb. Previous studies have shown that the temperature-induced cell-proliferation arrest caused by loss of HCF-1 activity in hamster-cell line tsBN67 can be bypassed through the inactivation of pRb by the adenovirus E1A oncoprotein and SV40 large T antigen,

indicating that one role of HCF-1 is to counter the activity of pRb in cell cycle inhibition.[8,9] Recent findings indicate that this opposition may be direct as pRb and HCF-1 can bind to E2F1 simultaneously in what is proposed as a repressive (pRb) to activating (HCF-1) transition complex during the G1 to S phase progression (**Fig. 1B**).[23] These studies led Mani and Fay to hypothesize that a similar antagonistic regulatory relationship may exist in worms .[26] They identified SUP-35, a new member of the RMD (regulator of microtubule dynamics), as the transcriptional regulator of novel protein PHA-1. PHA-1 regulates morphogenesis of pharynx early on in development. They proposed that *C. elegans* E2F ortholog, EFL-1, may partner with LIN-35/pRb in the regulation of SUP-35. Using the conserved ortholog of HCF-1 in C. elegans, they showed that HCF-1 functionally antagonizes LIN-35/pRb in the regulation of sup-35 in a complex regulatory network, which functions to control organ morphogenesis. Therefore, the regulatory relationship between pRb and HCF-1 that exists in mammals seems to be conserved in worms.

HCF-1 may be involved in regulation of pRb activity through another pathway involving Miz-1.[27] Miz-1 can activate the promoter of the cyclin-dependent kinase inhibitor p15INK4b, which inhibits pRb inactivation by phosphorylation. HCF-1 can repress Miz-1 activation of p15INK4b gene transcription, suggesting that HCF-1 indirectly promotes pRb inactivation by phosphorylation.[27] Interestingly, HCF-1 is also involved in regulation of pRb expression.[28] During myogenesis, upon induction of differentiation, HCF-1 is recruited to the pRb promoter and up-regulates the expression of pRb by co-activating GABP.[28] RNAi-mediated knock-down of HCF-1 results in inhibition of pRb up-regulation as well as myotube formation. Therefore, HCF-1 may be involved in regulating pRb at several levels, suppressing the function of this tumor suppressor in cycling cells and promoting its expression during differentiation.

Even though the pRb family of pocket proteins has three members—pRb, p107and p130—the regulatory relationship of HCF-1 may be partial to pRb, as HCF-1 has not been found in complex with other pocket proteins like p130.[23,29] On the contrary, HCF-1 binding site in E2F4 overlaps the pocket-protein binding site, suggesting that pocket-protein and HCF-1 association with E2F4 is

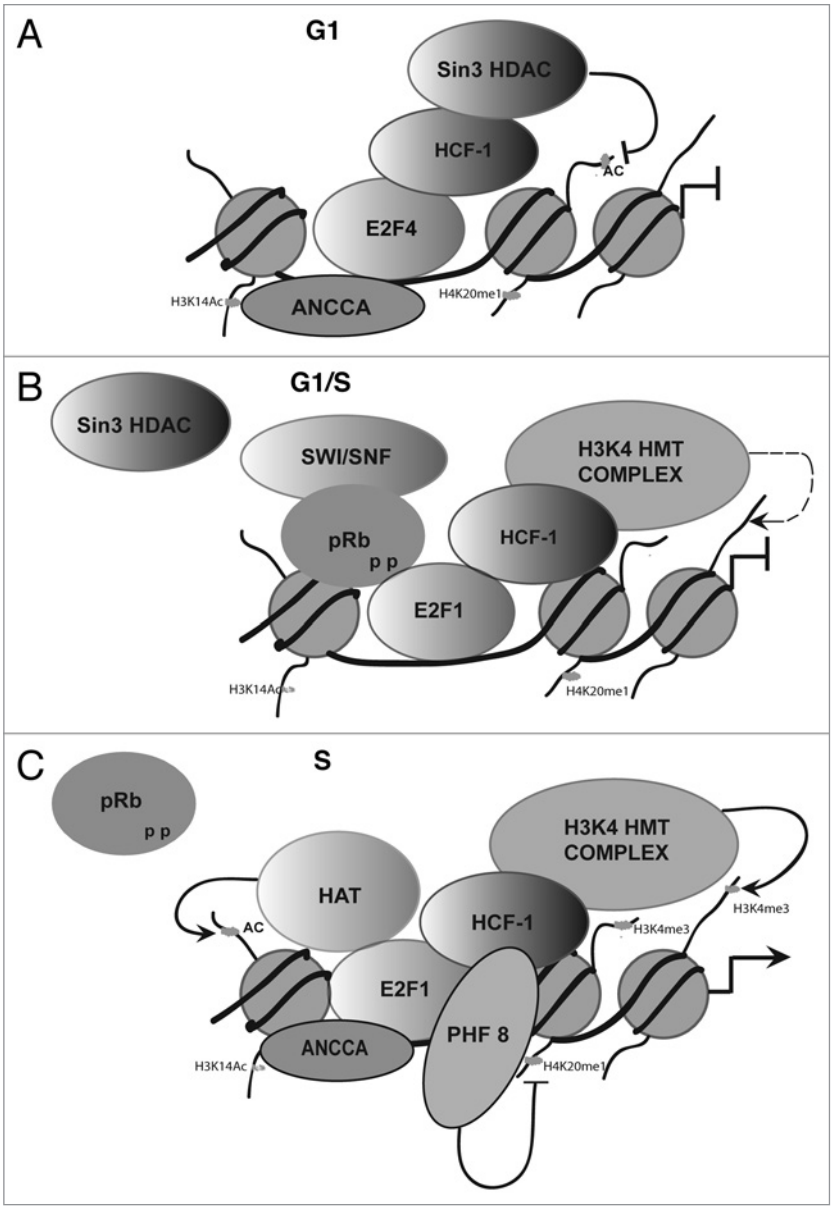

Figure 1. Model for E2F-HCF-1 complexes during the cell cycle. This model illustrates the interactions of HCF-1 with various members of E2F family during the cell cycle and the different co-factors associated with them. (A) During early G_1 phase, HCF-1 interacts with E2F4 and recruits Sin3 HDAC to E2F-responsive promoters. We speculate that this mechanism of repression is independent of pocket proteins. ANCCA binds to E2F-promoters in late mitosis. However, we do not know if HCF-1 and ANCCA co-occupy these promoters at this time. (B) This model proposes that HCF-1 forms an intermediate complex with pRB-E2F, where pRb has undergone phosphorylation by cyclin D/CDK4 but still remains bound to E2F. As the G_1 to S phase transition progresses, this intermediate complex is freed of pRb by subsequent phosphorylation by cyclin/CDK complex thereby switching from repressive (pRb) to activating (HCF-1) E2F-complex.[23,37] (C) Here we speculate the co-factors associated with E2F1 during S phase. ANCCA gets recruited to chromatin by binding to H3K14ac mark. Here it facilitates the loading of E2F to the chromatin. HCF-1 binds to E2F to promote the activation of S-phase genes by recruiting H3K4 HMT (MLL/Set1) and stimulating H3K4 trimethylation of gene promoters. PHF8 binds to H3K4 me2/3 mark and interacts with HCF-1. It removes the repressive H4K20 me1 marks at these promoters. Previous reports have shown that several histone acetyltransferase (HAT) are required for E2F activity.[38-41]

Table 1. Table summarizing histone residues and modifications which affect the E2F-responsive promoters

Histone residue	Type of modification	Modifying protein complex	Cofactors	Effect on the E2F-responsive promoter	Associated with E2F protein
H3K4	Di- and Tri-methylation	MLL	WDR5, Ash2L, HCF-1	Activation/recruitment of co-factors	E2F1
		Set1	WDR5, Ash2L, HCF-1	Activation/recruitment of co-factors	E2F1
H4K20	Demethylation	PHF8	HCF-1	Activation	E2F1
H3K14	Acetylation	HAT		Activation/recruitment of co-factors	E2F1
H3K9	Acetylation	HAT		Activation/recruitment of co-factors	E2F1
	Deacetylation	Sin3/HDAC	HCF-1	Repression	E2F4

Modifying complexes and their co-factors on E2F promoters are listed.

mutually exclusive. Although pRb has been best characterized for its repressive E2F-dependent functions that contribute to cell cycle control, there is emerging evidence that pRb has additional targets and performs multiple functions not common to other pocket proteins.[30] Given the multi-dimension nature of HCF-1-pRb relationship, it is tempting to speculate that HCF-1 may also participate in such pRb functions.

Interactions with PHF8. Recently, HCF-1 was found in another multi-protein complex containing E2F1, Set1 and PHF8.[31] PHF8 contains a Plant Homo domain (PHD) and Jumonji C domain, and functions as a demethylase for H3K9 mono- and dimethylated (H3K9me1/2), H3K27 di- (H3K27me2) [32] and H4K20 monomethylated (H4K20me1) .[31] PHF8 interacts with the HCF-1_N subunit and PHF8 siRNA like HCF-1 siRNA induces cell-proliferation arrest. During the G1 to S phase transition, PHF8 is recruited to selected E2F-responsive promoters, where it removes the repressive H4K20me1 mark. PHF8 recruitment to these promoters coincides with decrease in H4K20me1 levels and binding of L3MBTL1—a repressor protein that has been shown to associate with H4K20me1.[33] Further, PHF8 is recruited to its promoters via the interaction of its PHD domain to H3K4me2/3. PHF8 knockdown was accompanied with impaired recruitment of HCF-1 and Set1 along with decreased levels of H3K4 trimethylation on E2F-responsive promoters, whereas HCF-1 knockdown did not impair PHF8 recruitment. As PHD finger proteins strongly bind H3K4me3 and knockdown of WDR5 led to displacement of PHF8 from rDNA, it is not very clear how in this case HCF-1 knockout, which has been shown to recruit H3K4 HMT complex to these promoters, did not impair PHF8 recruitment.[32] Nevertheless, this study shows how the same protein complexes (E2F1/HCF-1/Set1/PHF8) may be modulating chromatin at various levels (H3K4 methylation and H4K20 demethylation) to activate transcription (see **Table 1**).[31, 23]

HCF-1 and PHF8 may be involved in regulation of more than one phase of cell cycle. Liu et al. suggest that as cells enter mitosis, timely dissociation of PHF8, triggered by its phosphorylation by CDK1/cyclin B1 complex, and accumulation of H4K20me1 primarily by increased activity of methyltransferase Pr-Set7, facilitates loading of Condensin II complex on the DNA.[34] Interestingly, loss of HCF-1 leads to up regulation of Pr-Set7 and perturbs the balance between H4K20 mono- and dimethylation mark.[21] These results suggest that both proteins—HCF-1 and PHF8—play a crucial role in maintaining proper levels of H4K20 monomethylation at the onset of mitosis. Only future experiments can reveal the extent of their involvement and if they regulate H4K20 mono methylation through the same pathway.

Interactions with ANCCA. The cell may start preparing for G1/S transition right after it exits mitosis. A recent report shows that, the AAA+ ATPase ANCCA (AAA nuclear co-regulator cancer-associated protein)/ATAD2 may be involved in such a function. ANCCA is recruited to the chromatin late in mitosis by interacting with acetylated lysine 14 of histone 3 (H3K14ac) via its bromodomain.[35] The authors suggest that ANCCA facilitates in loading of E2F1 to the chromatin and subsequent assembly of the HCF-1-MLL complex on the E2F-responsive promoters that leads to gene activation. In support of this model, ANCCA interacts with E2F1, E2F2, E2F3 and E2F4 directly, and siRNA knockdown of ANCCA affects expression of key cell cycle E2F target genes. ANCCA depletion results in a significant decrease in the H3K4me3 mark and chromatin occupancy of E2F1, HCF-1 and MLL complex, suggesting that ANCCA may be crucial for the assembly of E2F1 protein complex at G1 to S phase transition.[35] However, recent reports from Farnham laboratory showed that N- and C-terminal domains of E2F1, involved in protein-protein interaction, do not participate in targeting E2F1 to the chromatin.[36] Therefore, it remains unclear how ANCCA may be involved in loading of E2F1 to chromatin. Perhaps ANCCA does not recruit E2F1 to chromatin directly by protein-protein interactions but influences the local chromatin state rendering it favorable for E2F1 to bind to DNA. In any case, this model brings to lights the importance of distinctive histone modifications like H3K14ac and H3K9K14ac in recruitment of cofactors to E2F-responsive gene promoters (**Table 1**).

Conclusions

It is becoming exceedingly clear that E2F transcription is not as limited as it appears in our text-book models, but utilizes an array of proteins and histone modifications to activate or repress genes involved in cell proliferation. HCF-1 acts as a cofactor to E2F protein in distinct multi-protein complexes. HCF-1 containing E2F complexes can undergo a switch in composition to act as either an activator or a repressor making a clear classification of HCF-1 into either category difficult. The HCF-1 complexes can act as "writers" and "readers" to a variety of histone

marks, adding another layer of regulation to the already complex E2F pathway. The role of E2F pathway is well recognized in cancer. Now, activities of HCF-1 in promoting oncogenesis are coming to light. Therefore, it is all the more essential to understand the full extent of HCF-1 involvement in E2F regulation, the range of such diverse E2F-HCF-1 complexes and their precise role during the cell cycle.

Acknowledgments

We thank W. Herr for his support in our new ventures. Z.Z. is supported by research fellowship from Council of Scientific and Industrial Research and S.T. by Ramalingswamy Fellowship, Department of Biotechnology.

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