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Review Article

F-Box Proteins in Epigenetic Regulation of Cancer

Jia Shen and Charles Spruck*

Tumor Initiation and Maintenance Program, Sanford Burnham Prebys Medical Discovery Institute, USA

Abstract

Epigenetic abnormalities are now realized as important as genetic alterations in contributing to the initiation and progression of cancer. Recent advancements in the cancer epigenetics field have identified extensive alterations of the epigenetic network in human cancers, including histone modifications and DNA methylation. F-box proteins, the substrate receptors of SCF (SKP1-Cullin1-F-box protein) E3 ubiquitin ligases, can directly and indirectly affect the balance of epigenetic regulation. In this brief review, we discuss our current understanding of F-box proteins in cellular epigenetic regulation and how dysregulation of these processes contribute to cancer development.

***Corresponding author**

Charles Spruck, Tumor Initiation and Maintenance Program, Sanford Burnham Prebys Medical Discovery Institute, 10901 North Torrey Pines Road, La Jolla, CA, 92037, USA, Tel: 858-646-3100; Fax: 858-713-6274; Email: cspruck@sbpdiscovery.org

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ABBREVIATIONS

SCF: SKP1-Cullin1-F-box protein; CRLs: Cullin-RING ligases; AML: Acute Myeloid Leukemia; PRC: Polycomb-Repressive Complex; NSCLC: Non–Small Cell Lung Cancer; PcG: Polycomb Group; DUSP3: Dual-specificity Phosphatase 3; HDAC3: Histone Deacetylase 3; FBXW: F-box with the WD40 repeat domains; FBXL: F-box with the leucine-rich repeat domains; FBXO: F-box with domains not fully characterized; JmjC: Jumonji C; MEF: Mouse Embryo Fibroblast

INTRODUCTION

Cancer poses a rising threat to human health, with the estimated number of Americans with a history of cancer predicted to surpass 20 million within the next 10 years [1]. Cancer cells harbor global epigenetic alterations, which cooperate with genetic mutations in tumor development [2]. Epigenetic abnormalities include global changes in DNA methylation, histone modification patterns, and altered expression profiles of chromatin-modifying enzymes. These changes contribute to the inappropriate activation or inhibition of various signaling pathways, which participate in cancer initiation, progression, invasion, and metastasis [3-5].

It is well documented that F-box proteins function as substrate receptors for the SCF-type E3 ubiquitin ligase, which plays important roles in regulation of cell proliferation [6,7], migration and invasion [8-10], metabolism [11,12], angiogenesis [13,14], cell death [15-17], and DNA damage response [18-20]. In addition, recent studies have reported putative roles for several F-box proteins in cellular epigenetic regulation, and dysregulation of these F-box proteins and their associated functions could contribute to tumorigenesis. In this review, we provide an overview, based on our current knowledge, of F-box proteins in the regulation of cancer epigenetics.

THE F-BOX PROTEIN FAMILIES

In mammals, the largest family of E3 ubiquitin ligases is the Cullin-RING ligases (CRLs), of which SCF ligases are the best characterized. Humans express 69 different F-box proteins, which are categorized into three sub-families based on the presence of defined domains: FBXW- WD40 repeats, FBXL- leucine-rich repeats, and FBXO- undefined domains [21]. The protein-protein interaction domains of F-box proteins mediate substrate recognition, with each F-box protein targeting a unique set of substrates, each harboring unique 'degron' motifs.

F-box proteins in regulation of cancer epigenetics

Epigenetic alterations promote altered gene function, contributing to malignant cellular transformation. F-box proteins have been shown to directly and indirectly affect cellular epigenetics. FBXL10 (also known as Ndy1 or KDM2B), an F-box protein that binds CpG-rich promoters in the mammalian genome, has been shown to exert both histone ubiquitylation and histone demethylase activities [22,23]. FBXL10 contains an N-terminal Jumonji C (JmjC) domain, followed by a CXXC zinc finger, a plant homeodomain finger (PHD), an F-box domain, and 8 leucine-rich repeats. Several lines of evidence have shown FBXL10 is overexpressed in many human cancers including acute myeloid leukemia (AML) [24], seminomas [25] and pancreatic ductal adenocarcinomas [26]. Kottakis et al., [27] showed knockdown of FBXL10 expression in a panel of human tumor-derived cell lines induced G_1 phase delay and senescence and/or apoptosis. In addition, forced overexpression of FBXL10 in hematopoietic stem cells caused an acceleration of the G_0/G_1 to S phase transition and development of myeloid or B-lymphoid leukemia [28]. FBXL10 was shown to directly bind to CpG islands throughout the genome via its CXXC motif, and interact with Ring1B and Nspc1 to form a non-canonical Polycomb Repressive

Complex 1 (PRC1), which lead to the gene repressive modification H2AK119 mono-ubiquitination (H2AK119ub1) [22,29]. H2AK119ub1 is significantly correlated with poorer prognosis in patients with pancreatic ductal adenocarcinoma [22,29]. PRC1-dependent H2AK119ub1 also leads to recruitment of PRC2 and trimethylation of histone H3 on lysine 27 (H3K27me3) [30], which is a pivotal mark in the establishment of repressive chromatin. FBXL10 expression promotes cell proliferation and bypass of the senescence barrier in primary cells, in part by counteracting the senescence-associated down-regulation of EZH2, a PRC2 component, leading to global and Ink4a/Arf locus-specific up-regulation of histone H3K27me3 [31-33]. On the other hand, depletion of FBXL10 was shown to cause upregulation of Arf in MEFs, which suggests FBXL10 might accelerate cell proliferation by inhibiting the Arf tumor-suppressor pathway. In addition, FBXL10 was also found to demethylate histone H3 dimethylated at lysine 36 (H3K36me2), which is required for initiation and maintenance of acute myeloid leukemia. He et al., [34] found FBXL10 decreases transcription of the tumor suppressor p15Ink4b through demethylation of H3K36me2 near the gene promoter. Tzatsos et al., [26] demonstrated another potential mechanism by which FBXL10 could drive tumorigenesis. Utilizing gene expression arrays and ChIP assays, they showed FBXL10 repressed developmental genes by interacting with Polycomb Group (PcG) proteins at transcriptional start sites, and activated mediators of protein synthesis and mitochondrial function genes by interacting with the MYC oncogene and another histone demethylase FBXL11 (also known as KDM2B and JHDM1A).

FBXL11 and FBXL10 share conserved JmjC and CXXC domains, both of which can catalyze the demethylation of H3K36me2. Like FBXL10, FBXL11 can also bind CpG islands, though it preferentially recognizes non-methylated CpG DNA, and binding is interrupted by CpG methylation [35]. In addition, FBXL11 does not associate with PcG proteins so its function appears different from that of FBXL10. FBXL11 is frequently overexpressed in non-small cell lung cancers (NSCLCs) and this is correlated with poor prognosis [36]. FBXL11 was also shown to be indispensable for tumorigenicity and invasiveness of FBXL11-overexpressing NSCLC cells, and knockdown of FBXL11 expression decreased the growth and invasive capabilities of NSCLC cells in mouse xenograft models. Mechanistically, FBXL11 was shown to activate ERK1/2 through epigenetic repression of dual-specificity phosphatase 3 (DUSP3) via demethylation of H3K36me2 [36]. Another study showed FBXL11 transcriptionally repressed histone deacetylase 3 (HDAC3) through demethylation of H3K36me2 in FBXL11-overexpressing NSCLC cells [37]. Additionally, analysis of FBXL11 knockout mice showed its depletion resulted in significant loss of H2A ubiquitylation, indicating an important role in regulation of histone ubiquitination [38]. However, it is unclear how the ubiquitylation functions of FBXL10 and FBXL11 coordinate with their demethylase activities, though they are the only F-box proteins known to exhibit demethylase activity [39].

In addition to directly binding chromatin to regulate epigenetic modifications, F-box proteins can also indirectly influence cancer epigenetics through the direct targeting of epigenetic regulators for ubiquitin-dependent proteolysis. KDM4A (also known as JMJD2A) is a demethylase that targets histone H3K9me2/3 and H3K36me2/3 leading to transcriptional repression. KDM4A has been shown to play an important role in gene expression [40], cellular differentiation [41, 42] and cancer [43]. Tan et al., [44] and Van Rechem et al., [45] showed that FBXO22 and FBXL4 independently regulate KDM4A proteolysis. FBXO22 regulates cellular histone H3 marks and KDM4A target gene transcription by controlling KDM4A protein levels. FBXO22 depletion was shown to stabilize KDM4A resulting in a significant reduction in the abundance of H3K9me3 and H3K36me3 on promoters of KDM4A's target genes. Since KDM4A plays a role in cancer development, FBXO22 seems to be a tumor suppressor. Furthermore, the F-box protein β-TrCP1 (FBXW1A) mediates the ubiquitin-dependent proteolysis of UHRF1, which plays a critical role in maintaining DNA methylation patterns during DNA replication and its deregulated expression correlates with cancer development. In this case, β-TrCP1 exerts its tumor suppressor function to maintain genomic stability by targeting UHRF1 degradation in response to UV-induced DNA damage [46].

DISCUSSION AND CONCLUSION

Our current knowledge demonstrates F-box proteins play pivotal roles in the epigenetic regulation of cancer, mediated through E3 ubiquitylation-dependent or -independent mechanisms (Table 1). Since only a handful of epigenetic regulator F-box proteins have been functionally characterized, research in this field is limited and many key questions remain unaddressed. For example: Do additional F-box proteins also regulate cancer epigenetic regulation? What are the upstream signaling pathways that control the functions of F-box proteins involved in regulation of cancer epigenetics? How do the epigenetic regulatory functions of F-box proteins coordinate with their ubiquitylation functions? Addressing these questions will be crucial to deciphering the importance of this protein family in the regulation of cancer epigenetics and whether it can be effectively targeted for therapeutic benefit for cancer treatment.

Table 1: F-box Proteins in Regulation of Cancer Epigenetics.

F-box proteins	Targets	Functions	References
FBXL10	CpG islands	Histone H2A	[22,23,29,31]
	and histone	ubiquitylation and	
		histone H3	
		demethylation	
FBXL11	CpG islands	Histone H2A	[36-38]
	and histone	ubiquitylation and	
		histone H3	
		demethylation	
FBXO22	KDM4A	Regulation of	[44]
		KDM4A stability and	
		target gene	
		transcription	
FBXL4	KDM4A	Regulation of	[45]
		KDM4A stability	
β-TrCP1	UHRF1	Maintenance of DNA	[46]
		methylation patterns	
		under DNA damage	

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