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Review

FoxM1: At the crossroads of ageing and cancer

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Abstract

Forkhead transcription factors are intimately involved in the regulation of organismal development, cell differentiation and proliferation. Here we review the current knowledge of the role played by FoxM1 in these various processes. This particular member of the Forkhead family is broadly expressed in actively dividing cells and is crucial for cell cycle-dependent gene expression in the G2 phase of the cell cycle. FoxM1 plays a crucial role in insuring the fidelity of the cell division process, as inhibition of FoxM1 activity results in serious aberrancies during mitosis, such as frequent chromosome missegregation, defects in cytokinesis and overt aneuploidy. FoxM1 expression also appears to be tightly correlated with the proliferative rate of a cell. For example, FoxM1 is one of the most significantly down-regulated genes in prematurely aged human fibroblasts (Progeria syndrome), while elevated expression of FoxM1 is seen in most human carcinomas. These observations suggest that interference with FoxM1 activity may contribute to the increase in mitotic errors seen in human diseases such as cancer and early onset of ageing diseases. In this review, several aspects of FoxM1 function will be discussed, as well as their implication in tumorigenesis.

Keywords: Cell cycle; Transcriptional regulation; Mitosis; Checkpoints; Forkhead

Contents

1. Introduction

Cell cycle progression is, at least partly, controlled by transcriptional programs. These have been well studied in yeast, in which many cell cycle-regulated genes displaying a periodical

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expression pattern have been identified [1]. These genes can be grouped in clusters of co-regulated genes, which are usually controlled by a single transcription factor complex [2,3].

In the yeast *Saccharomyces cerevisiae*, two major cell cycle transcriptional programs have been identified: the G1/S transcriptional program that depends on the activity of the SBF/MBF transcriptional complex, and the G2/M transcriptional program referred to as the CLB2 gene cluster that depends on the activity of the FKH/Mcm1/Ndd1 transcription regulatory complex [4–8]. The SBF/MBF transcriptional complex regulates the expression of genes involved in DNA replication, while CLB2 gene cluster encodes about 33 genes involved in entry and execution of mitosis, among which the Clb1 and Clb2 mitotic Cyclins and the Cdc5 Polo-like kinase [8]. Expression of genes in the CLB2 gene cluster is controlled by two closely related forkhead-like transcription factors Fkh1 and Fkh2 in complex with their transcriptional co-activators Mcm1 and Ndd1 [5–8]. Evidence that a similar G2/M transcriptional program is also present in higher eukaryotes is scarce, but a recent study done in our lab has uncovered a role for the FoxM1 forkhead transcription factor in the regulation of numerous mitotic genes that overlap with the CLB2 cluster [9]. Although FoxM1 and the yeast forkhead transcription factors Fkh1 and Fkh2 do not share any apparent homology at the nucleotide level, both seem to regulate a similar G2/M transcriptional program in eukaryotes. However, whether cofactors, such Ndd in yeast, participate in FoxM1-mediated transcription, remains to be determined. In this review we will discuss the function of FoxM1 as a transcriptional regulator and how this is linked to regulation of cell cycle progression and carcinogenesis.

1.1. FoxM1

1.1.1. FoxM1 is a transcription factor of the Forkhead family

FoxM1 is a transcription factor of the Forkhead family. It is also known in the literature as Trident (in mouse), HFH-11 (in human), WIN or INS-1 (in rat), MPP-2 (partial human cDNA) or FKHL-16. In order to keep some clarity and homogeneity, and according to the proposed nomenclature of the Forkhead family members [10], we will refer to it as FoxM1 in this review.

The Forkhead family comprises a large number of transcription factors defined by a conserved DNA binding domain called Forkhead or winged-helix domain. The FoxM1 gene was cloned by screening cDNA libraries with degenerate primers for homologues with a conserved Forkhead DNA-binding domain [11–13]. The FoxM1 gene was revealed to encode a Forkhead transcription factor family member that exhibits 45% identity in the DNA-binding domain with five of its closest related Forkhead members, namely FoxA3 (HNF-3γ, FoxC1 (fkh-1), FoxF2 (FREAC-2), FoxK1 (ILF) and FoxN2 (HTLF) [11]. The FoxM1 C-terminal region was found to have homology (76% identity) with a human partial cDNA encoding an open reading-frame of 221 amino acids, termed MPP-2. MPP-2 stands for MPM-2-reactive phosphoprotein-2 and was identified after screening a lymphoblast-derived cDNA library with the MPM-2 monoclonal antibody, which binds specifically to epitopes on mitotic proteins that are phosphorylated in a phosphoserine-proline dependent manner [14]. FoxM1 binds DNA in vitro through the consensus site TAAACA [11]. This motif shares the core sequence recognized by other members of the forkhead family [11,15]. In particular, repeats of these motifs, in alternating orientation, were often characterized within the selected binding sequences for FoxM1 [11].

1.2. FoxM1 is alternatively spliced

The human FoxM1 gene is a 10-exon structure spanning approximately 25 kb on the 12p13-3 chromosomal band (telomeric position) [11]. Two exons, named exons Va and VIIa, also referred to as exon A1 (or rat exon 6) and A2 respectively, are alternatively spliced [11–13]. Exon Va encodes a 15 amino-acid insertion within the C-terminal part of the DNA binding-domain, and is not seen in any of the other Forkhead transcription factor family members. Exon VIIa represents a 38 amino-acid insertion within the C-terminus of the protein. Strikingly, in rat, one FoxM1 mRNA species also contains a small exon (exon 4) which appears to be exclusive to rat and is not present in other species. The presence of this exon leads to lower expression of the transcript [12].

Differential splicing of exons Va and VIIa in human FoxM1, gives rise to three classes of transcripts, class A containing both alternative exons, class B containing none of the alternative exons, and class C in which exon Va only is retained [13] (see Fig. 1). Both FoxM1B and C are transcriptionally active,

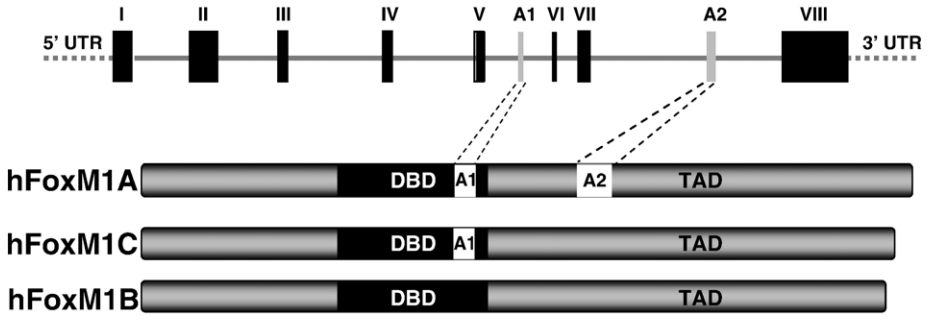

Fig. 1. Schematic representation of known splice variants of human FoxM1 protein. Two exons, named exon A1 and A2, are alternatively spliced in FoxM1 gene. Exon A1 encodes a 15 amino-acid insertion within the C-terminal part of the DNA binding-domain (DBD), and Exon A2 represents a 38 amino-acid insertion within the C-terminal transactivation domain (TAD) of the protein. Differential splicing of these exons generate three encoding FoxM1 isoforms, named FoxM1A, C and B.