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# Regulation of MCM7 DNA Replication Licensing Activity

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## 1. Introduction

Miniature chromosome maintenance (MCM) proteins were initially identified from autonomously replicating sequence in *Saccharomyces cerevisiae*. Mutations of some of these proteins such as MCM7 or MCM3 in yeast result in loss of the large chunk of yeast chromosomes. MCM7 cDNA encodes a 543-amino acid protein and is ubiquitously expressed in all tissues. Initiation of DNA replication is a complex process involving the concerted action of many proteins. A large body of studies indicate that MCM7 is a critical component of DNA replication licensing complex in the yeast and xenopus (Chong et al., 1996; Coxon et al., 1992; Dalton and Whitbread, 1995; Kearsley et al., 1996). Some studies suggest that MCM4, 6 and 7 complex contains DNA helicase activity (Ishimi, 1997; You et al., 1999). DNA replication licensing complex is multimeric and phase specific. In the yeast, DNA replication licensing proteins such as MCM2-7 and several replication origin binding proteins such as Cdc6 and Cdt1 forms DNA replication licensing complex in G1 phase to enable DNA replication and to promote cell cycle entry into S phase. Such complex, however, dissipates in the S, G2 and M phases to prevent re-firing of DNA replication, and thus protect the integrity of genomes. There is little interest in MCM complex as target for oncogenic or tumor suppressor pathway until the links of MCM7 over-expression and amplification to several human malignancies were found (Brake et al., 2003; Honeycutt et al., 2006; Kan et al., 2009; Ren et al., 2006).

## 2. MCM7 transforming oncogenic activity

Initial implication of MCM7 involvement in human malignancies is positive immunostaining of MCM7 in several human malignancies, including endometrial carcinoma (Li et al., 2005), melanoma (Gambichler et al., 2009), esophageal adenocarcinoma (Kan et al., 2009), colorectal adenocarcinoma (Nishihara et al., 2008), oral squamous cell carcinoma (Feng et al., 2008), glioblastoma (Facoetti et al., 2006), and thyroid cancer (Kebebew et al., 2006). Most of these studies used MCM7 as a proliferation marker to compare with the existing markers such as Ki-67 or PCNA. The first study addressing the oncogenic role of MCM7 came from genome analysis of prostate cancer. By performing a genome wide copy number analysis using biotin-labeled genome DNA on Affymetrix U133 2.0 chip (Ren et al., 2006) (figure 1). Ninety-two genes and expressed sequenced tags (ESTs) consistently had a two-fold or greater number of genome copies in the prostate cancer

specimens relative to matched blood cells ( $p < 0.01$ , using baseline analysis by Microarray Suite 5.0™). To determine whether these gene amplifications were associated with increased expression of the same loci, mRNA expression arrays were performed with the same tumor samples and matched normal prostate tissue adjacent to but separate from the tumor. Only five of the 92 potential amplifications had increased mRNA expression. Using SYBR-green quantitative PCR and fluorescence *in situ* hybridization (FISH) with bacterial artificial chromosome containing these genes, it has been confirmed that two of these genes were amplified in the prostate cancer specimens. One of these genes, MCM7, located at 7q21.3 and a component of DNA replication licensing complex, was found to be amplified 4 and 15 fold, respectively.

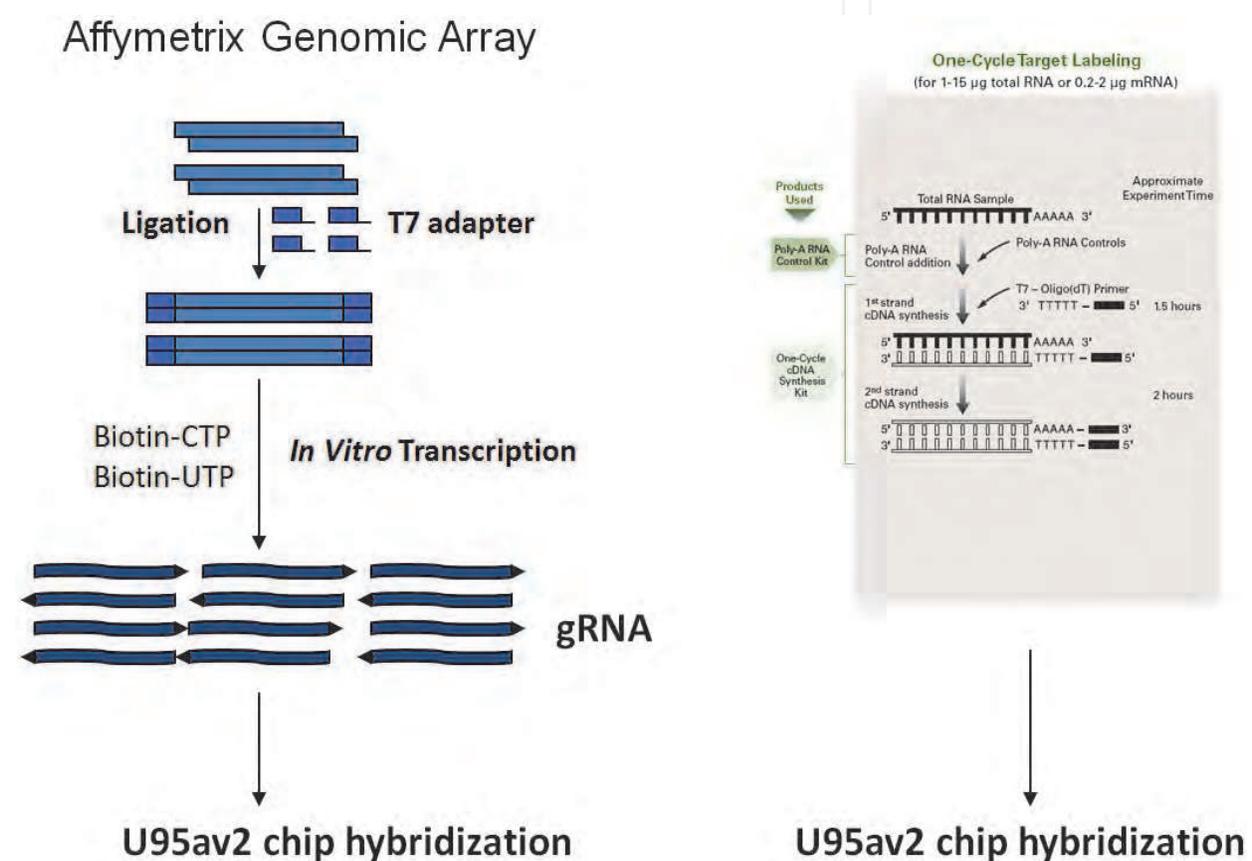


Fig. 1. Schematic diagram of genome hybridization on U133 2.0 chip. Left panel: Genome DNA from prostate cancer samples with matched blood were digested with Tsp509I restriction enzyme and ligated with an adaptor containing T7 promoter. In vitro transcription was then carried out to generate biotin-labeled gRNA. The gRNA was then fragmented and hybridized to HU133 2.0 chip for signal analysis. Right panel: Total RNA from matched samples of the left were reverse transcribed using T7-oligo dT (24) primer. After double-stranded cDNA synthesis, in vitro transcription using GTP, ATP, biotin-labeled UTP and CTP was then performed. The resulting cRNA was then fragmented and hybridized to U95av2 chip.

Subsequent validation analyses suggest that either copy number and/or protein level increase of MCM7 are associated with prostate cancer relapse and metastasis. To determine the prevalence of MCM7 amplification in prostate cancer, FISH analyses were performed on

74 prostate samples, including 58 cancers and 16 benign tissues (Figure 2). Nearly half, (26/58, 45%) of the prostate cancers had at least a doubling in the number of genome copies (compared to the centromere of chromosome 7) (Table 1). Meanwhile, none of the benign prostate tissues demonstrated a similar amplification. As further validation of these findings, SYBR-green quantitative PCR was performed on an additional 133 prostate samples, including 119 cancers and 14 normal tissues. In this analysis, fifty percent (59/119) of the prostate cancers had at least a 2-fold increase in the MCM7/ $\beta$ -actin ratio relative to DNA from benign prostate specimens. In the most up-regulated case, the MCM7/ $\beta$ -actin ratio in the cancer sample was 16-fold greater than control levels.

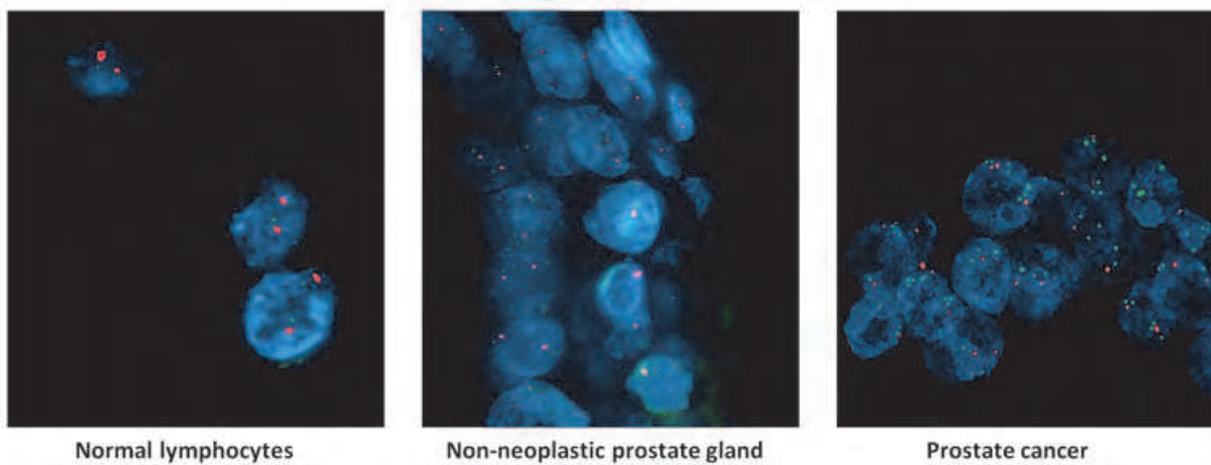


Fig. 2. MCM7 amplification and overexpression in prostate cancer. Images of fluorescence *in situ* hybridization (FISH) on normal lymphocytes, non-neoplastic prostate gland and prostate cancer. Chromosome 7 centromere is labeled with orange spectrum (orange), and MCM7 is labeled with fluorescein (green).

Amplification of MCM7 was associated with a significantly increased rate of prostate cancer relapse within 5 years of radical prostatectomy (defined as a detectable PSA): 76.5% (52/68) patients with MCM7 amplification relapsed compared to only 12.3% (7/57) of patients without MCM7 amplification ( $p < 0.0001$ , log-rank test) (figure 3A). Similar results were seen with MCM7 protein expression: 76.3% patients with  $\geq 2+$  MCM7 expression experienced a recurrence within 5 years after radical prostatectomy compared with only 26.5% patients with weak MCM7 expression ( $p < 0.006$ ) (figure 3B). The combination of MCM7 amplification and overexpression generated additional improvement in separating the two groups (Figure 3C).

Eleven clones of DU145 transfected with a constitutive MCM7 cDNA overexpression vector were characterized by Western blot analysis, and two with high MCM7 expression were chosen for subsequent analysis. Over a 6-h experimental period DU145 pCMV-MCM7 clones had twice the number of cells enter S phase (figure 3B), with cell proliferation being 50% faster than vector only controls (figure 3C). DU145 pCMV-MCM7 clones had a 2-fold higher level of invasiveness in Matrigel transmigration analysis compared to vector-only controls. *In vivo*, DU145 pCMV-MCM7 xenograft tumors were twelve times larger than vector-only control tumors, 2.58 cm<sup>3</sup> versus 0.22 cm<sup>3</sup>, respectively ( $p < 0.0001$ ), with a 50% mortality within 6 weeks of inoculation ( $p = 0.0063$ ). These findings are consistent with the clinical findings that increased MCM7 expression is associated with higher rates of local tumor invasion.

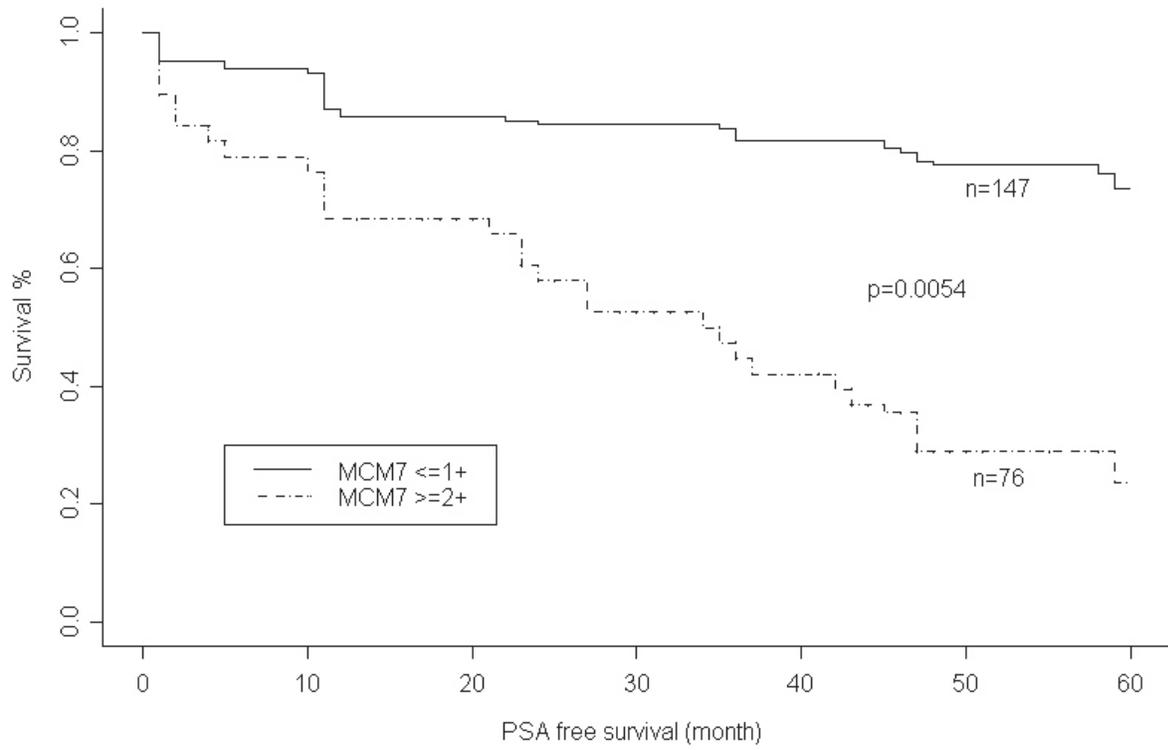
Case number	Gleason score	Pathology stage	MCM7/centromere	Relapse*
95T	7	T3a	6.67	Y
72T	7	T3a	6.42	Y
54T	9	T3b	6.1	Y
45T	6	T2b	5.49	Y
139T	8	T2b	4.2	Y
69T	6	T3a	4.15	Y
5T	7	T2b	3.97	Y
85T	7	T2b	3.77	Y
48T	8	T3a	3.5	Y
4T	9	T3b	3.3	Y
101T	6	T3a	3.11	Y
107T	6	T3a	3.11	Y
2213T	6	T3a	3.06	Y
42T	7	T3a	2.69	Y
214T	6	T3a	2.66	Y
3T	9	T3b	2.52	Y
2T	7	T3a	2.49	Y
147T	6	T3a	2.46	Y
68T	6	T2b	2.1	Y
22T	6	T3a	1.86	Y
7T	7	T3a	1.62	Y
93T	9	T3b	1.52	Y
6T	6	T2b	1.5	Y
641T	6	T2b	1.1	Y
56T	6	T2b	0.95	Y
39T	7	T3a	0.84	Y
40T	6	T3a	5.76	N
75T	6	T2b	5.55	N
911T	6	T3a	4.48	N
46T	7	T3a	4.47	N
83T	7	T2b	1.94	N
99T	8	T3a	1.82	N
13T	7	T2b	1.74	N
67T	9	T3b	1.64	N
1127T	6	T3a	1.58	N
M35	6	T2b	1.55	N
26T	6	T2a	1.54	N
11T	7	T2b	1.54	N
194T	6	T2b	1.37	N

82T	7	T3a	1.24	N
55T	6	T2b	1.18	N
91T	7	T2b	1.14	N
94T	7	T3a	1.13	N
96T	6	T2a	0.97	N
941T	6	T2b	2.17	U
M33	8	T3b	2.13	U
M29	7	T3b	2.05	U
217T	7	T3a	1.96	U
121T	6	T2b	1.86	U
M21	6	T2b	1.68	U
M24	6	T2b	1.64	U
853T	6	T2b	1.49	U
M28	8	T3b	1.39	U
998T	6	T2b	1.29	U
M36	7	T2b	1.14	U
M31	7	T3a	1.11	U
828T	6	T2b	1	U
M23	7	T2b	0.94	U
M2	Normal Prostate		1.2	N/A
A4	Normal Prostate		1.01	N/A
M4	Normal Prostate		0.9	N/A
P28	Normal Prostate		1.2	N/A
P91	Normal Prostate		0.89	N/A
P93	Normal Prostate		0.95	N/A
U-2	Normal Prostate		1.3	N/A
D-41	Normal Prostate		0.8	N/A
U-4	Normal Prostate		1.2	N/A
9	Normal Prostate		1	N/A
19	Normal Prostate		1.09	N/A
99	Normal Prostate		0.93	N/A
11	Normal Prostate		1.02	N/A
12	Normal Prostate		1.08	N/A
13	Normal Prostate		1.03	N/A
14	Normal Prostate		1.05	N/A

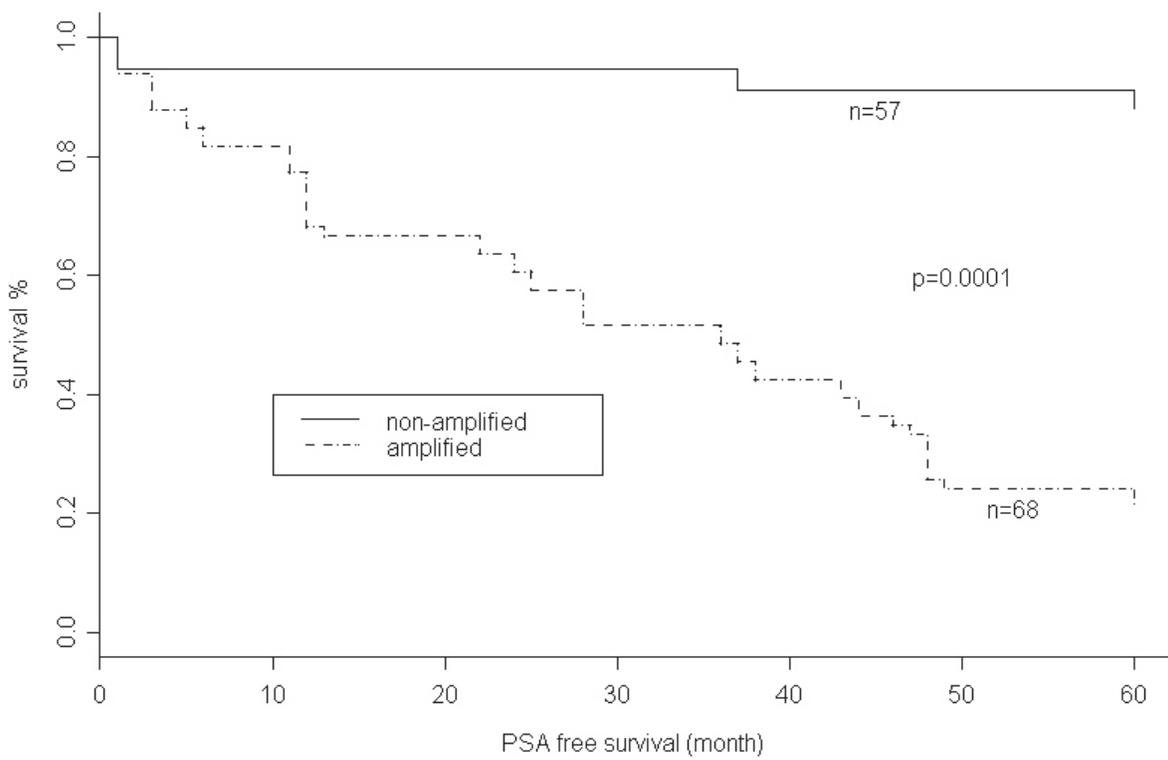
Y=yes; N-No; U-undetermined due to lack of follow-up; N/A-not applicable.

\*Determined by PSA relapse or physical evidences of metastasis within 5 years after prostatectomy.

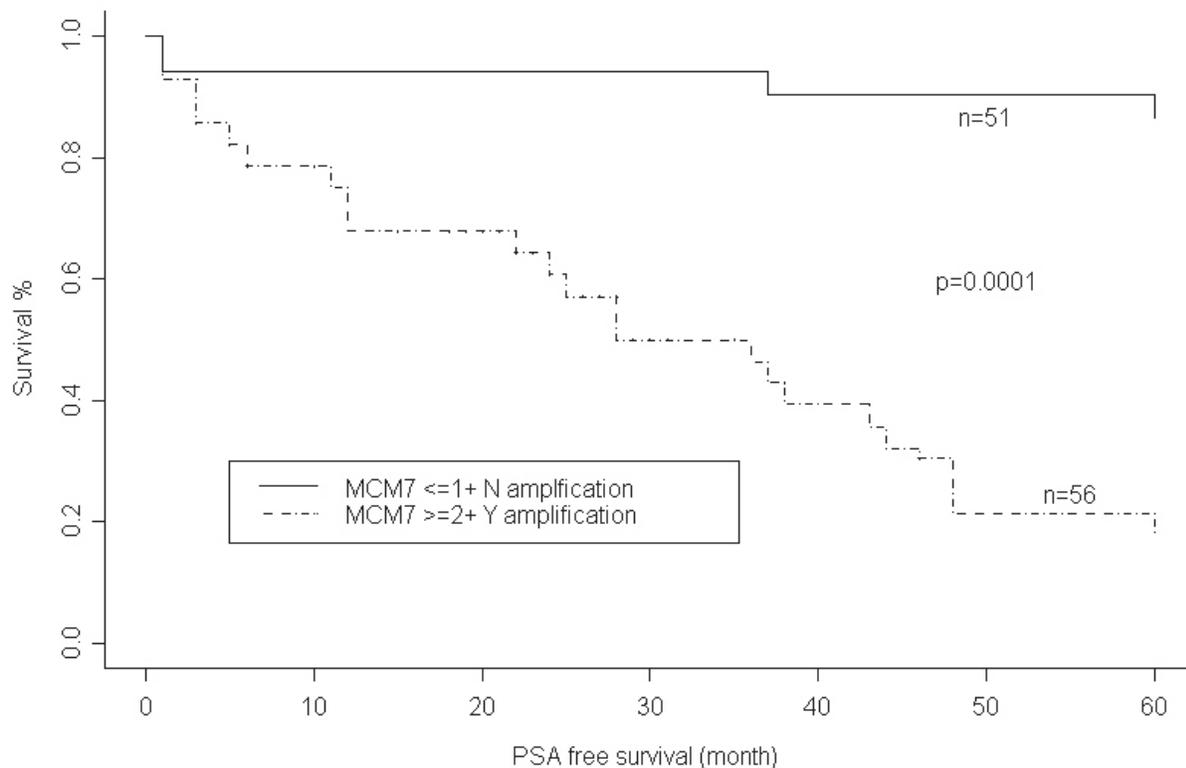
Table 1. FISH analysis of MCM7 amplification in primary prostate cancer



(a)



(b)



(c)

Fig. 3. MCM7 amplification and overexpression associated with prostate cancer relapse. A. Kaplan curves of samples from patients with clinical follow-up for 5-year period. The samples were divided by presence (Y) or absence (N) of MCM7 amplification based on FISH and/or quantitative PCR. Ratios of MCM7/Centromere or MCM7/ $\beta$ -actin  $\geq 2$  are considered an increase of MCM7 DNA. B. Kaplan curves of samples from patients with clinical follow-up for 5-year period. The samples were divided by MCM7 expression scores: scoring  $\geq 2+$  or  $\leq 1$ . C. Kaplan curves of samples from patients with clinical follow-up for 5-year period. The samples were divided by presence (Y) or absence (N) of MCM7 amplification and MCM7 overexpression.

Amplification of MCM7 was also found in esophageal carcinoma (Kan et al., 2009). The magnitude of MCM7 amplification correlates with the expression of MCM7, tumor grades and aggressiveness of the esophageal cancer (Kan et al., 2009). It is presumed that amplification of MCM7 is the driving force of MCM7 over-expression in primary human malignancies. When MCM7 was transgened in basal cells of skin of mice utilizing keratin promoter, the animals developed squamous cell carcinoma upon DMBA/TPA challenge versus complete negative results from the WT controls (Honeycutt et al., 2006). However, MCM7 does not play an initiator role in cancer development because organ specific MCM7 transgene mice develop no spontaneous cancer either in skin nor prostate model (Honeycutt et al., 2006; Poliseno et al.). The inability of MCM7 expression alone to initiate carcinogenesis could result from other negative feedback mechanisms that neutralize MCM DNA replication licensing in the cell, such as Rb or ILK signaling discussed later. Even though MCM7's transforming activity is clearly observed, strictly speaking, it does not fall into the

category of a typical proto-oncogene because it does not have a viral counterpart nor sequence mutations that render its oncogenic potential. MCM7 probably falls into the broadly defined oncogene category whose gain of oncogenic function is generated by epigenome or chromosomal numerical alterations.

### 3. MCM7 as target of oncogenic or tumor suppressor signaling pathways

The first significant signaling pathway targeting MCM7 was found by yeast two-hybrid screening analysis where the N-terminus of Rb bait probe binds with MCM7 (Sternier et al., 1998). Additional analysis suggests that other Rb homologues p107 and p130 also bind with MCM7 (Sternier et al., 1998). *In vitro* analysis indicates that the binding of MCM7 and Rb inhibits DNA replication. However, the biological significance of such interaction was not elucidated until 11 years later that interaction of Rb-MCM7 is essential for TGF $\beta$  induced blockade of entry into S phase (Mukherjee et al.). These studies suggest that MCM7 could be the main target of Rb in controlling cycle S phase check point (figure 4). This is because over-expression of MCM7 can reverse Rb inhibition effect, and peptide that interferes with MCM7/Rb binding but not other activity of Rb also reverses the Rb check point blockade. Another salient example of MCM7 as a target of a signaling pathway is androgen receptor signaling. It is well known that androgen receptor regulates cell growth and proliferation. However, most of the studies have been focusing on gene expression regulation which may play secondary role in controlling cell cycle progression. It was found later that AR interacts with MCM7 directly, and inactivates or activates MCM DNA replication licensing depending on the nature of ligands or their concentrations (Shi et al., 2008). Mutation of MCM7 that abrogates its interaction with androgen receptor but not its DNA replication licensing activity eliminates the pleiotropic effect of testosterone. Furthermore, androgen receptor mutant that does not bind with MCM7 can translocate into nucleus upon androgen stimulation but fails to induce cell proliferation or to enhance transcription of androgen dependent genes. It appears that both DNA replication activity and transcription activity of AR is dependent on its binding with MCM7. It is likely that AR serves as a co-replication factor that directs the MCM complex DNA replication licensing through its interaction with MCM7 (figure 4). One surprising finding in the analysis is that MCM7 also serves as a co-transcription factor for AR. There are several well read studies showing that transcription activity enhances DNA replication, and that transcription activity is dependent on DNA replication in eukaryotic cells (Marahrens and Stillman, 1992; Veldman et al., 1985). It remains to be seen whether MCM7 dependent transcription activity holds truth with other MCM7 interacting transcription factors. The MCM7 dependency of androgen receptor transcription activity suggests that androgen dependent gene expression could only occur in actively proliferating cells, since MCM7 is excluded from the nucleus during S, G2 and M phases, and it only re-enters the nucleus in G1 phase.

MCM7 also plays some critical role in mediating the function of cell membrane receptor. This is demonstrated in its interaction with integrin linked kinase (figure 4). It appears that MCM7 is a substrate of integrin linked kinase. The binding and phosphorylation of MCM7 N-terminus by integrin linked kinase reduce the binding of MCM7 with other DNA replication licensing factors, and lead to slow-down of cell growth (Han et al., 2010). The phosphorylation of MCM7 by integrin linked kinase proves to be a critical link to the tumor suppressor activity of integrin  $\alpha 7$ . Dominant negative mutant of integrin linked kinase

interrupts the integrin linked kinase/MCM7 interaction, and partly blocks the tumor suppression activity of integrin  $\alpha 7$ . MCM7 mutant that lacks the integrin linked kinase binding motif operates DNA replication licensing similar to that of wild type but is unresponsive to integrin  $\alpha 7$  signaling. These findings suggest that MCM7 could be the end target of many oncogenic or tumor suppressing signaling pathways. Depending on the nature of these interactions or modification of MCM7, it may lead to increased or decreased DNA replication licensing activity of MCM complex, and guides the cells into either higher level of proliferation or cell growth arrest.

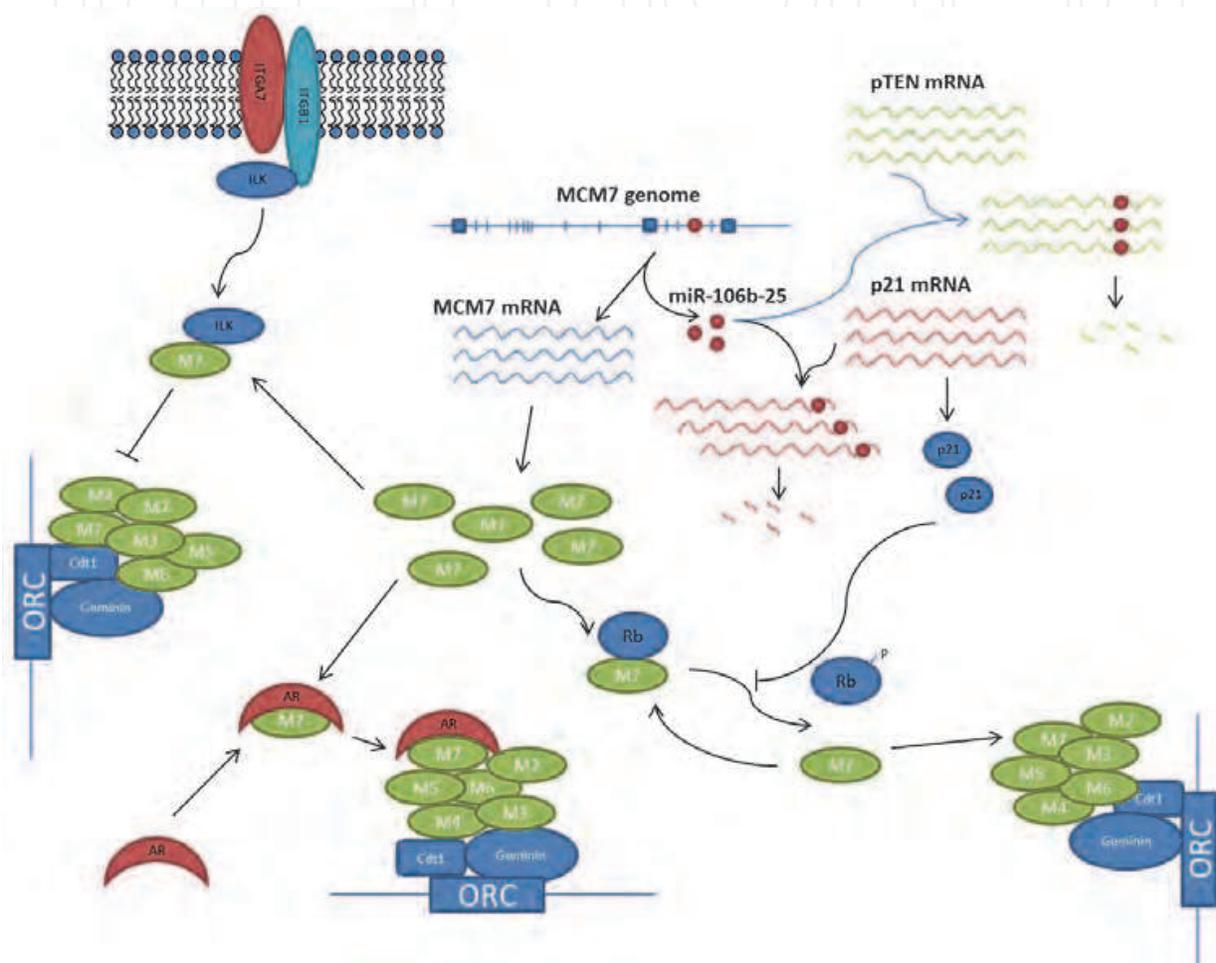


Fig. 4. Diagram of MCM7 oncogenic signaling. Fifteen exons and miR106b-25 oncogenic miRNA cluster of MCM7 genome were transcribed into MCM7 mRNA and miRNA 106b, 93 and 25. Two prong pathways were directed at promoting DNA replication: Degradation of critical tumor suppressor genes p21 and pTEN mRNA by miR106b-25 cluster, and increase of DNA replication licensing by MCM7 protein. Androgen receptor (AR) promotes DNA replication by enhancing MCM7 replication licensing activity. Integrin  $\alpha 7$  inhibits DNA replication through inhibition of MCM7 activity.

#### 4. Transforming miRNA cluster in MCM7 genome

A unique feature of MCM7 genome is that it contains an intronic miRNA miR-106b-25 cluster in intron 13, which includes miR-106b, miR93 and miR-25. miR-25 is highly

homologous to miR-32, a onco-miRNA, while miR-106b and miR-93 belong to the family of miR-17. All three members of miR-106b-25 cluster are abundantly expressed in most of the prostate cancer cell lines. Similar to their host gene MCM7, amplification and up-regulation of all members of miR-106b-25 cluster are found in several human malignancies including esophageal and prostate cancers (Ambs et al., 2008; Kan et al., 2009; Petrocca et al., 2008a; Poliseno et al., ; Sikand et al., 2009). These miRNAs target multiple tumor suppressor genes, and shut down their expression levels (figure 4). One of the most notable examples is pTEN gene expression. miR-25 and miR-93 expression decrease pTEN protein levels, and result in activation of AKt pathway (Poliseno et al.). The expression of miR106-25 cluster increase tumorigenesis in both anchorage-independent assay and xenografted tumors in animal model. The mice with knock-in prostate specific MCM7 and miR-106-25 cluster develop cancer like dysplasia in mice, while mice with pure MCM7 knock in do not seem to develop dysplasia without carcinogen challenge. One may interpret such observation as miR-106-25 cluster function as tumor initiator by knocking down pTEN in mice, while over-expression of MCM7 serves as a mechanism for the development of invasive phenotype. miR-106b-25 cluster appears more versatile than knocking down just one tumor suppressor gene. Several studies suggest that miR-106 and miR-25 target p21, Bim and E2F1 (Ambs et al., 2008; Kan et al., 2009; Petrocca et al., 2008a; Petrocca et al., 2008b). These targets and their relationship have been clearly demonstrated in prostate cancer, esophageal adenocarcinoma and gastric cancer. Inhibition of E2F1 by miR-106b and miR-93 in gastric cancer cell lines partially blocks TGF $\beta$  induced apoptosis (Petrocca et al., 2008b). Interestingly, E2F1 is a strong stimulator of MCM7 locus transcription. As a result, a negative feedback loop of MCM7/miR-106b-25 is formed. Such feedback loop may serve to limit the excessive cell death induced by TGF $\beta$  in physiological condition, and thus achieves a balance of cell growth and cell death. In the event of malignancies, amplification of MCM7 locus may bypass such negative feedback loop, and tips the balance to cell survival. Targeting on p21waf and bim by miR-106b and miR-25 were demonstrated in both esophageal and prostate cancers. Application of inhibitors of miR-106, miR-93 or miR-25 inhibits tumorigenesis both *in vitro* and *in vivo*. With these targets that all appear critical for the oncogenic activity of miR-106b-25 cluster, it is not easy to analyze the contribution of each of these pathways to carcinogenesis since there is a lack of experiments to block off each of the pathways to offset the oncogenic activity of miR-106b-25 cluster. Generally speaking, miR-25/93-pTEN pathway is compelling because of the inverse correlation of pTEN expression and miR-106b-25 miRNA levels in primary and mouse tumor samples, the animal model initiating prostate cancer with MCM7/miR-106b-25 cluster transgene showing clear down-regulation of pTEN expression and concomitant increased level of miR-106b-25 cluster expression, and consequent Akt pathway activation. It would be of interest to see how much oncogenic phenotype will be reversed if these animals are transgened with pTEN, or p21 or BIM or E2F1 gene construct lacking the miR-106b-25 target sequences in their 3' untranslated regions.

## 5. Potential therapeutic target

MCM7 is essential for any cell that undergoes proliferation. This poses a dilemma for MCM7 gene targeted therapy. Nevertheless, a report indicates that shRNA targeting MCM7 in xenografted PC3 and DU145 tumors in mice dramatically reduces tumor volume, rate of metastasis and fatality (Shi et al., 2010). The drawback of this analysis is that the shRNA

target may not recognize the MCM7 sequence from mice since the target sequence is intended for human MCM7. Nevertheless, the study is a proof of principle that MCM7 knockdown is a potential effective approach in combating prostate cancer, particularly those with MCM7 amplification and over-expression. In light of double oncogenic effect of MCM7 genome cluster, it may be more effective if a shRNA is designed to neutralize the effect of miR-106b, miR-93 and miR-25 onco-miRNA. This can be accomplished with large dosage of morpholino oligonucleotide specific for these onco-miRNAs. These RNase resistant oligonucleotides have a clear advantage over genome approach that it will not interfere with the genome structure of a cell but have long lasting presence once they are taken. Furthermore, there is no evidence suggesting that knocking down of these miRNAs adversely affects the survival of normal cells.

## 6. Abreviation

M7-MCM7; M6-MCM6; M5-MCM5; M4-MCM4; M3-MCM3; M2-MCM2; ITGA7- Integrin  $\alpha$ 7; ILK-integrin linked kinase; AR-androgen receptor; ORC-origin recognition complex.

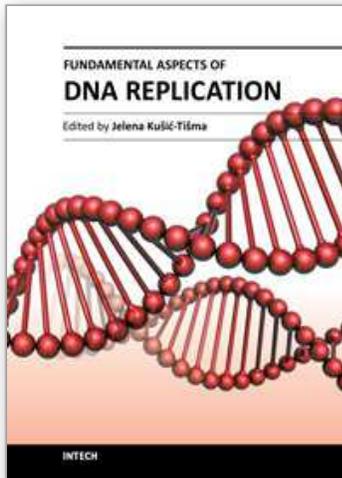
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DNA replication, the process of copying one double stranded DNA molecule to produce two identical copies, is at the heart of cell proliferation. This book highlights new insights into the replication process in eukaryotes, from the assembly of pre-replication complex and features of DNA replication origins, through polymerization mechanisms, to propagation of epigenetic states. It also covers cell cycle control of replication initiation and includes the latest on mechanisms of replication in prokaryotes. The association between genome replication and transcription is also addressed. We hope that readers will find this book interesting, helpful and inspiring.

### **How to reference**

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