MCM2-7 complex: a review

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Abstract

New cells are formed from preexisting cells through an ordered series of events called cell cycle. As the control of this cycle is fundamental for genome integrity, multiple proteins regulate this process. We currently know that the MCM2-7 complex has a major role in DNA replication in the cell cycle, in particular regarding proliferation. The immunohistochemical identification of the proteins in this complex on tissues may be useful, as they could be used as biomarkers and would help us understand one of the biological mechanisms affected in cancer processes. Our aim is to collect the existing evidence regarding the members of the MCM2-7 complex, since these proteins could be effective biological cell proliferation markers, which would help practitioners make accurate diagnosis, prognosis and future therapeutic targets of lesions that are mainly neoplastic, especially in the oral mucosa.

Keywords: MCM2-7 complex, cell proliferation, tumors.

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Introduction

New cells are formed from preexisting cells through an ordered series of events called *cell cycle*. The cycle is divided into four phases: G1, S, G2 and M (Fig.1). Although the cycle can be addressed conceptually from any phase, it is usually analyzed from the G1 phase. This is the phase immediately after mitosis (M): the cell grows because of different events that include synthesis of RNA, proteins and other cell elements. The following stage is called S phase, where the cell replicates the entire chromosomal DNA, leading to duplication. The centrioles and the centrosome also duplicate, which will be essential for the M phase (mitosis) to occur in this cycle.

The next phase is called G2 and separates the S phase from mitosis. Here, there is rapid cell growth and DNA security molecular mechanisms are activated. They are used to search for errors in the DNA sequence. If such errors are detected but not corrected, mechanisms that prevent the cycle from developing are triggered. When the absence of errors is verified and G2 is complete, the M phase begins, which is where the process of mitosis occurs. This is divided into four stages (prophase, metaphase, anaphase and telophase), where the mother diploid cell produces two diploid daughter cells [1].

Some cells may remain in a state of basal metabolism without dividing or replicating their DNA. These cells are in G0 phase or in a quiescent state (Fig. 1), which can be a transitory state, where the cell is stimulated and re-enters the cell cycle, or a permanent state, where the cell never divides again [1].

Cell proliferation is an increase in the number of cells, a result of cell division. It is more active during embryogenesis and the development of an organism, but continues throughout life, as it is necessary for tissue homeostasis [1].

As the control of this cycle is fundamental for genome integrity, multiple proteins regulate this process. If this regulation is lost, diseases such as cancer may appear, where a cell makes up a cell line with unlimited and uncontrolled cell proliferation capacity due to genetic mutations [1].

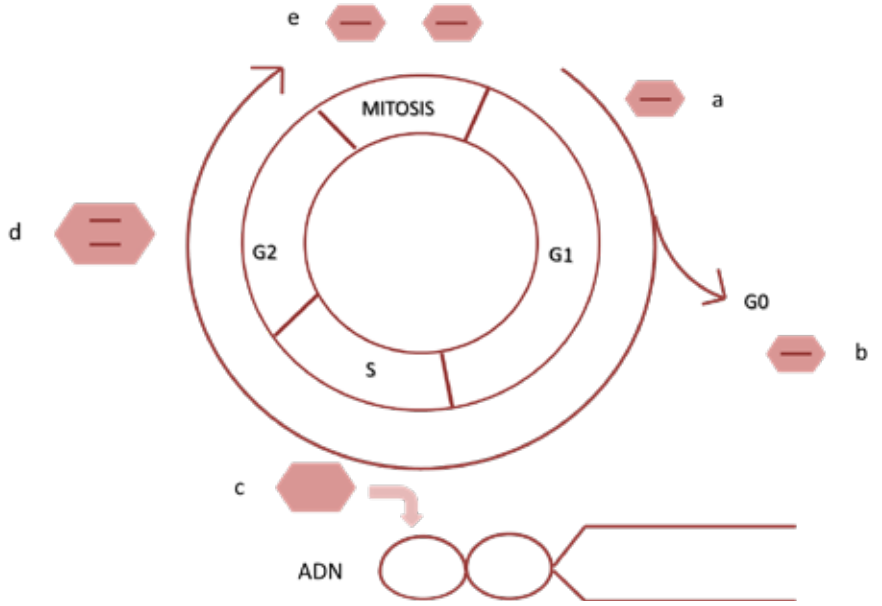

Fig. 1: Cell cycle. a- G1 phase: the cell enters the cell cycle. b- G0 phase: the cell is in a quiescent state. c- S phase: the cell duplicates its DNA. d- G2 phase: the cell with duplicated DNA. e- Mitosis: cell division into two daughter cells.

Identifying the proteins involved in the cell cycle allows us to use them as biomarkers of cell proliferation (through immunohistochemistry, essential technique in the pathological diagnosis of cancer), which are useful for the diagnosis, prognosis and treatment plan of different neoplasms, as several experimental research studies suggest.

Our aim is to collect evidence of the MCM2-7 complex (biological proteins involved in the cell cycle and its control) and to identify and mark defective mitosis, particularly in pre-malignant or potentially cancerous oral pathologies such as leukoplakia (in its different forms) actinic cheilitis, lupus erythematosus and lichen planus, all of which tend to become cancerous lesions.

Methods

We conducted a literature review in the electronic database PubMed throughout 2017. The review included articles published in the previous 15 years and reference texts on the subject reviewed, using the following terms in English: "complex MCM2-7, cellular proliferation, cancer". We included 45 articles in English to guide this literature review.

Development

MCM2-7 complex (minichromosome maintenance)

The MCM2-7 complex was recognized in 1980. It has a toroidal structure and includes six different proteins (MCM2, MCM3, MCM4, MCM5, MCM6, MCM7) [(2)].

The MCM2-7 complex is part of the pre-replicative complex, so it plays an essential role in DNA replication [(3)] (Fig. 2). Therefore, it would be useful to know how it participates in the cell cycle to understand one of the biological mechanisms affected in cancer processes.

Pre-replication complex

The MCM7 protein, along with MCM2, MCM4 and MCM6, have DNA-helicase activity, so they could act as enzymes that unwind DNA.

The pre-replicative complex is formed near the end of mitosis and in early G1 phase. It includes the origin recognition complex (ORC), cell division cycle 6 (Cdc6) and MCM2-7 [(4-5)] (Fig. 2). This complex marks the DNA fragment where replication will start. In the S phase of the cell cycle, the pre-replicative complex is activated, giving rise to DNA replication [(6-7)] (Fig. 2). Once replication is complete, the complex dissolves and its components are destroyed [(4)].

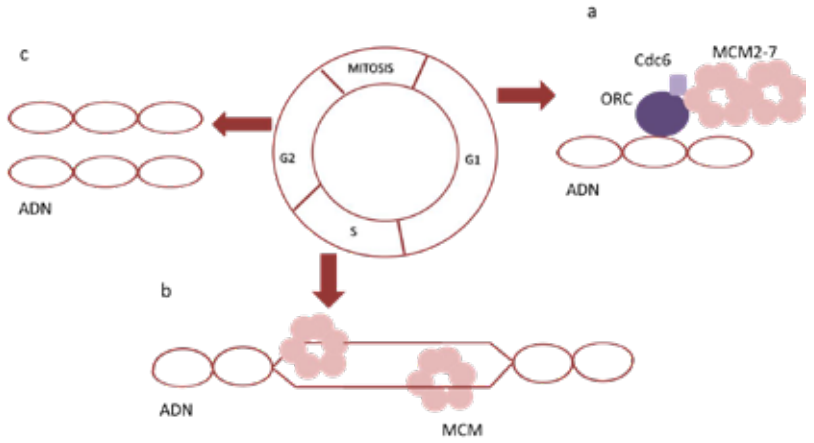

Fig. 2: a- Pre-replicative complex formed. b- Active complex, DNA replication. c- Two DNA strands, complex dissolves.

The activity of MCM proteins is highly regulated by a cyclin-dependent kinase (CDK), which has low levels at the end of mitosis and during early G1. Therefore, it promotes the formation of the pre replicative complex and increases at the end of phases S and M. This leads to the phosphorylation of the MCM2-7 complex components, making them exit the cytoplasm and degrade [4-5].

MCM functions

As mentioned above, the complex has an essential role in DNA replication [8-9].

1. It starts the replication process at the right time, for which it must change its three-dimensional structure. When inactive, the MCM2-7 complex has a reversible discontinuity in its toroidal structure. As MCM2 and MCM5 bind, they close this discontinuity, which allows the MCM2-7 complex to activate [10-11] (Fig. 3).

Fig. 3: a- Active complex b- Inactive complex

2. Helicase function: after the MCM2-5 discontinuity is closed, the MCM2-7 complex begins to unwind the two DNA strands for replication to occur. Helicase activity has been demonstrated in vitro for the MCM4, 6 and 7 subcomplex [12]
3. It stops replication: if damage is detected in the DNA, the MCM2-7 complex stops helicase activity [13].
4. It ensures the entire DNA is replicated: cue to the large size of the chromosomes, thousands of sites are necessary for replication to begin [7]. However, only some of the multiple sites that have the pre-replicative complex are used. The others remain dormant, and if there is replicative stress, they are activated, which is why all the DNA must be replicated [14]
5. It prevents repeated DNA replication [15]. Once the DNA is replicated, they are exported to the cytoplasm and degrade their components [4].

According to Nguyen 2000, all the proteins that form the MCM2-7 complex have the same localization pattern in the cell cycle, and once replication is complete, they are exported to the cytoplasm.

However, contrary to this author, more recent genetic and biochemical studies show that the MCM2-7 complex subunits have different functions [16-18].

As mentioned above, helicase activity has been demonstrated in vitro for the MCM4, 6 and 7 subcomplex [12], while MCM2, 3 and 5 are responsible for activating and deactivating the complex [10-11].

Given the high activity of the MCM2-7 present in the cells during the cell cycle, and the fact that these proteins are absent in quiescent cells, the different proteins in the MCM2-7 complex could be good markers of cell proliferation [19], possible biological markers for diagnosis and prognosis [20-21] and future therapeutic targets [22]. It has been shown that several tumor suppressors can inhibit MCM 2-7 activity [22].

Role in carcinogenesis

Overexpression of MCM proteins has been demonstrated in a variety of neoplasms. MCM2 expression is increased in bladder carcinoma [23], ovarian adenocarcinoma [24], **proliferative verrucous leukoplakia** [25], oligodendrogliomas [26], renal cell carcinoma [27] and breast cancer [28]. Also, MCM3 in papillary thyroid carcinoma [29], MCM4 in small cell lung cancer [30] and cutaneous melanoma [31], MCM5 in gastric adenocarcinoma [32], bladder carcinoma [23], ovarian adenocarcinoma [24], squamous cell carcinoma of the skin [33], cervical cancer [34], **squamous cell carcinoma of the buccal mucosa [35] and proliferative verrucous leukoplakia** [25], MCM6 in hepatocellular carcinoma [36] and MCM7 in prostate cancer [37], colon cancer [38] and pulmonary adenocarcinoma [39].

These are just some of the many studies that have shown the overexpression of the different proteins of the MCM complex in various neoplasms. Therefore, they conclude that these proteins could be good cell proliferation markers.

It has been shown that the deregulation of MCM proteins is an early event in tumor development. It is therefore suggested that these biomarkers can be very useful in the primary diagnosis and monitoring of the tumor [28, 40-41].

According to Williams, 1998, MCM5 has high sensitivity and specificity to detect malignant precursor cells by using immunoperoxidase or immunofluorescence in Pap smears. Williams proposes this diagnostic method as an additional test besides Pap smear to decrease false-negative rates [40]. Furthermore, Williams, 1998 and Strober 2002 understand that high levels of MCM5 in urine are highly predictive of bladder cancer [40-41].

There are several authors who conclude that these proteins are superior to conventional markers such as Ki-67, since they have higher expression and therefore better diagnostic sensitivity [25, 42-43].

Higher expression of this complex, compared to Ki67 expression can be explained in two ways: As mentioned above, we find more pre-replicative complexes than the ones used to initiate replication. The others remain dormant to be activated if there are problems in some of the replication forks. This number of pre-replicative complexes, and therefore of the MCM2-7 complex, is what is referred to as "excess MCM" [42]. Ki-67 is expressed in the middle of the G1 phase [44], while as mentioned above, the pre-replicative complex and therefore MCM2-7 is expressed at the beginning of the G1 phase [45].

Conclusions

As shown, MCM complex proteins and, more specifically MCM 2 and 5, could act as good biological markers of cell proliferation, as is clear from the results of the research conducted. Altered or defective tissue immunoexpression would be an effective complementary diagnosis and prognosis tool, as well as future therapeutic targets. Therefore, we must improve our knowledge in the area, both from a functional perspective and regarding its participation in various biological processes. This would help practitioners detect neoplastic lesions early, including oral cancer, in their clinical practice, and therefore select the right therapy.

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