The Libyan International Medical University

Faculty of Basic Medical Science

Cell Cycle Regulation of Stem Cells by MicroRNAs

Khalid Mehana

Supervised by: Dr. Amal Elnaily

Assisted by: Dr. Nawar Montaser

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Abstract:

A non-coding RNA (ncRNA) is an RNA molecule that is not translated into a protein. MicroRNAs (miRNAs) are a class of small non-coding RNA molecules involved in the regulation of gene expression. They play a role in the fine-tuning of essential biological processes such as proliferation, differentiation, and apoptosis in many types of cells. It has been postulated that several miRNAs target transcripts that directly or indirectly coordinate the progression of the cell cycle within stem cells. Furthermore, past studies have shown that altered expression levels of miRNAs can contribute to pathological conditions, such as cancer, due to the loss of cell cycle regulation. However, the exact mechanism by which miRNAs control the cell cycle within stem cells is still incompletely understood. In this review, we will discuss current knowledge of the regulatory role of miRNAs in the progression of the cell cycle within stem cells and how specific miRNAs may control cell cycle associated molecules in embryonic and somatic stem cells.

Introduction:

The cell cycle is divided into four phases in eukaryotes: Gap 1 (G1), Synthesis (S), Gap 2 (G2), and Mitosis (M). During G1, also known as the first interphase, the cell synthesizes necessary proteins for DNA replication and continuous growth. This is followed by DNA replication which occurs in the S phase. The DNA integrity is then checked in the G2 phase, or second interphase, and at this point the cell is growing and preparing for cell division. Finally, during the M phase, the cell divides into two daughter cells. After division the cell can either reenter the G1 phase or go into the quiescent state. This state of reversible cell cycle arrest is known as the G0 phase and helps maintain cellular homeostasis.[(1)]

Stem cells are cells with the unique ability to differentiate into multiple cell lineages and self-renew. This is done by an asymmetric division during which one daughter cell is a copy of the stem cell and the other daughter cell differentiates. They are divided into two broad types: embryonic stem cells (ESCs), which are only present

during the earliest stages of development, and somatic (or adult) stem cells, which appear during fetal development and persist throughout life. Embryonic stem cells are pluripotent, meaning they can differentiate into all possible cell types of the three germinal layers. Somatic stem cells, on the other hand, are multipotent therefore they can only differentiate into cell types of their specific tissue or organ.[2]

Materials and Methods:

A research defined publications of interest as articles reporting the effect of miRNA on the cell cycle in stem cells. I have searched in the Pubmed database using the following search terms: MicroRNA, Cell cycle, Stem cells, ESC, Somatic stem cell. The search was set to include full text articles but excluded conference abstracts, editorials, and notes.

Discussion and Result:

In response to mitogenic stimuli, a protein called cyclin D increases and forms heterodimers with enzymes called cyclin dependent kinase (CDK4/6). This complex subsequently phosphorylates proteins of the retinoblastoma (RB) family including the RB tumor suppressor protein (pRb). The E2F family are a group of genes encoding for transcription factors E2F-1, E2F-2, and E2F-3. These are targets for the RB family and pRb is a negative regulator of E2F genes. Hypophosphorylation of pRb inactivates E2F transcription factors, inhibiting the G1 to S phase transition. While hyperphosphorylation of pRb leads to release of E2F from E2f/pRB complex and contributes to G1/S transition. [1]

CDK proteins are key regulators of the cell cycle progression. The transition through the S phase is regulated by the Cyclin E-CDK2 complex, in contrast, Cyclin B-CDK1 controls the G2/M transition. Cyclin dependent kinase inhibitor (CDKI) proteins such as p21/Cip1, p27/Kip1, and p57/Kip2 block the activity of Cyclin E-CDK2 and Cyclin A-CDK1. In addition, proteins of the INK4 family, including p16/INK4A,

p15/INK4B, p18/INK4C, and p19/INK4D inhibit the Cyclin D-CDK4/6 activity which is an important mechanism for tissue homeostasis that leads to cell cycle arrest and prevents tumorigenesis. The p53-p21 signaling pathway also plays a role in the G1/S and G2/M transitions and loss of p53 is the main reason for genomic instability. [1]

Embryonic Stem Cells (ESCs)

ESCs have a short G1 phase and a prolonged S phase. This leads to a shorter cell cycle compared to somatic stem cells and could be due to a plethora of causes. The idea that the phosphorylation status of pRb as a regulator of the G1 phase length, the reduction or absence of DNA damage response pathways in ESCs, and low expression levels of negative regulators of cell cycle progression have all been explored and implicated. Previous studies have demonstrated a distinct and abundant expression of microRNAs (miRNAs) in ESCs. The most prominently expressed are miR-290-295, miR-302, miR-17-92, miR106b-25, and miR-106a-363 arranged in homologous clusters, so-called polycistronic loci. These miRNAs are called the regulators of the embryonic stem cell cycle (ESCC). In general ESCC miRNAs facilitate G1/S transition through the suppression of RB proteins. They have also been demonstrated to directly regulate the expression of p21/Cip1 and cyclin E-CDK2 regulatory molecules in murine embryonic stem cells (mESCs).[2]

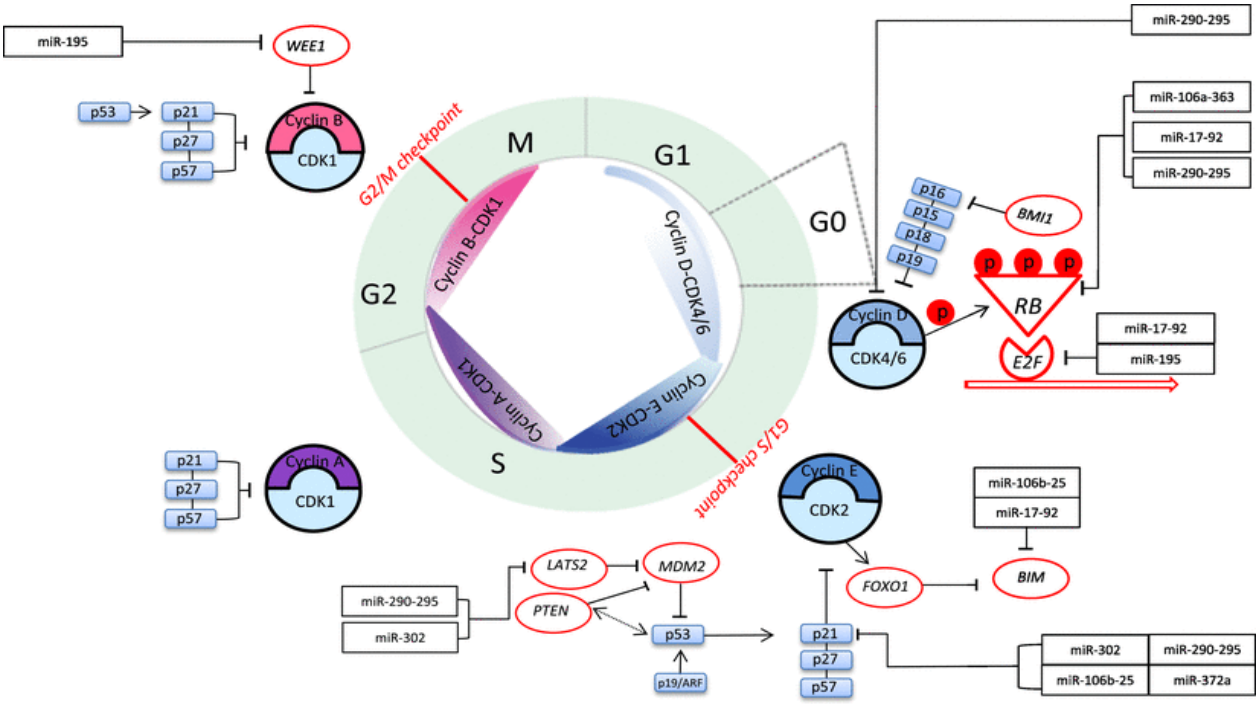

Figure 1

Fig.1

: **An overview of cell cycle regulation in ESCs by miRNA.** As shown, a network that progresses the cell through the four phases of the cell cycle is formed by key regulatory elements including cyclins, CDKs, and CDKI. MiRNAs either directly or indirectly target the cell associated components. Inhibition of E2F by miR-92 and miR-195 leads to a shorter G1 phase by decreasing the transcription of multiple transcription factors and proteins (e.g. E2F-1, E2F-2, E2F-3, and CDK2). In addition, the expression of the main G1/S and G2/M checkpoint regulator p53 is decreased indirectly by the action of miR-290-295 and miR-302 on LATS2. Furthermore, p21 expression is reduced by indirectly through the reduction in p53 and directly via miR-290-295, miR-372a, miR-302, and miR-106b-25 which leads to inhibition of cyclin E-CDK2 activity, and therefore facilitates G1/S transition. Additionally, the pro-apoptotic gene BIM is targeted by miR-106b-25 and miR-17-92 resulting in a reduction of cells entering apoptosis.[(1)]

Somatic (Adult) Stem Cells:

MiRNAs have been revealed to be important regulators of proliferation, survival, and differentiation in somatic stem cells through studies conducted on tissue specific Dicer-knockout mice. Since somatic stem cells are multipotent, the role played by the miRNAs differs depending on the specific tissue to which they belong. In the following paragraphs, the discussion will revolve around hematopoietic and mesenchymal stem cells.[3]

The self-renewal aspect of HSC can be highlighted by the difference in rate of proliferation in adult HSC and fetal HSC, adult HSC are usually quiescent while fetal HSC are highly proliferative. This is due to the LIN28 gene and the HMGA2 both of which have self renewal functions. The LIN28 gene leads to downregulation of the miRNA let-7 which subsequently down regulates HMGA2. Thus the concentration of this miRNA directly controls the self renewal capabilities of the LIN28/HMGA2 pathway in HSC. Depending on presence of specific surface markers, HSC can be classified as long term hematopoietic stem cells (LT-HSCs) and short term hematopoietic stem cells (ST-HSCs).[1]

Mesenchymal stem cells (MSC) originate in the bone marrow stroma but can be found in multiple tissue types such as adipose tissue, bone, skeletal muscle, cartilage, and tendon. Investigations through Drosha and Dicer knockdown studies have revealed a significant increase in the number of cells in the G1 phase and a reduction in the proliferation rate of these MSCs. A decrease in pRB and increase in p16 and p15 levels has also been documented. Other studies have revealed inhibition of MSC proliferation and cell cycle arrest through the actions of miR-16's action on Cyclin E. Mir-143 has also been shown to be a negative regulator of the MSC cell cycle by targeting ERK5 (member of MAPK family), which leads to the decreased expression of Cyclin D and CDK6 causing a reduction in cell entry into the S phase.[3]

Conclusion:

The potential role of miRNAs in the regulation of the cell cycle in stem cells is supported by a growing body of evidence. It is well established that abnormalities in the cell cycle are associated with tumorigenesis which makes it all the more crucial to unravel the molecular interaction and complex mechanisms involved and discover any possible clinical applications to this field of study. Either through a deeper understanding of tumor suppression through interactions of miRNA with tumor suppressor genes or miRNA actions on self renewal mechanisms, the possibilities seem endless.

Bibliography:

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