New Insights Into In Vivo Regulation Of Cell Cycle

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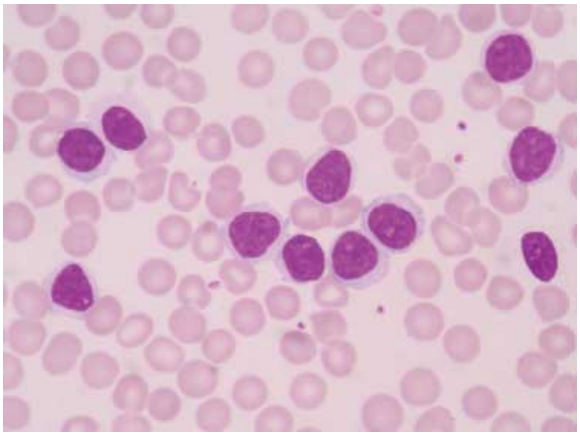


A new study published in Cell Reports shed light into how cell division cycles are regulated at the organism level. Cuitino et al. combined tissue imaging and artificial intelligence to study the expression of certain key regulators of cell division in intact organisms.

Mammalian cell cycle and its implications in cancer

Mammalian cells proliferate by progressing through four distinct cell cycle stages: G0/G1, S, G2 and M. Regulation of these cell cycle stages is crucial for determining the shape and size of tissue in mammals and other multicellular organisms. An intricate network of signaling pathways regulates this process, taking into account cues from inside and outside the cell such as the type and number of neighboring cells, cell size, and stage of development. Uncontrolled cell proliferation is a hallmark of cancer. Various cell cycle regulators are implicated in cancer and hence, are attractive targets in cancer therapy.

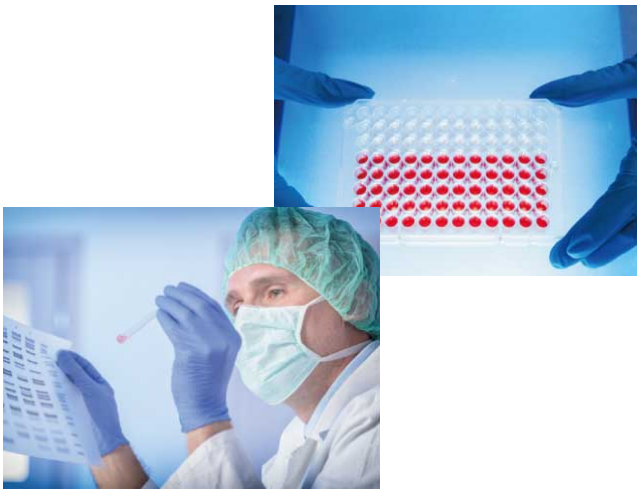
Cell cycle regulation – a coordinated act by a multitude of proteins

The mammalian cell cycle regulation is coordinated by a host of regulatory proteins. The major players include cyclin-dependent kinases (CDKs) and their catalytic partners – cyclins, retinoblastoma protein (RB) and the E2F family of transcription factors. Cyclin D and CDK4/6 play a key role in cell-cycle progression by phosphorylating and inactivating the retinoblastoma protein, a tumor suppressor that restrains G1- to S-phase progression. This results in the activation of transcription by the E2F family of transcription factors.

E2F family of transcription factors – proteins that control the cell cycle roller coaster

The journey of a cell through the different stages of cell cycle is a roller coaster ride of proteins involved. Expression of a set of genes increases during one phase of the cell cycle and the expression of the same set of genes decreases during a later cell cycle stage. This 'up and down' of gene expression ensures correct progression through the cell cycle. The E2F transcription factors play a critical role in this roller coaster ride.

There are at least nine different E2F transcription factors in mammals with either activation (switch-on) or repressive (switch-off) functions. These transcription factors are the "on-off-switch modules of cell division" explains the corresponding author of the study, Gustavo Leone, Ph.D. Dr. Leone and her team unraveled the spatio-temporal expression or 'when and where' these transcription factors are expressed in mammalian cells.



As discussed above, abnormalities in cell cycle regulatory mechanisms can lead to diseases such as cancer. Several cell cycle regulators are linked to cancer, including some well-characterized therapy targets. The link between E2F transcription factors and cancer are well-established as deregulation of E2F-dependent transcription is seen in most human neoplasias. These new findings are, therefore, a step forward in the quest to understanding the complex relationship between cell cycle regulation and cancer.

Poor in vivo understanding of cell cycle-regulated transcription

Previous studies on these key regulators of cell cycle were done using in vitro cell culture systems. While cell culture systems are invaluable tools to study fundamental biological mechanisms and cancer pathways, in vivo studies conducted at the organ- or organism-level give us the big picture. This study revealed the big picture of how E2F-dependent transcription factors function in vivo, particularly “when and where” they are expressed in mammals during embryonic and adult development.

"Not knowing when and where ‘on and off’ switches for cell division are expressed is like having paint with no canvas. Now we have the canvas, and thus the cellular context, for how these proteins behave within cells in the body," says Dr. Leone

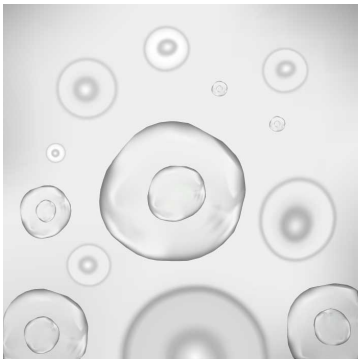
The study highlights the presence of two E2F functional modules

The study revealed two distinct E2F transcriptional modules - one module that controls cell-cycle-dependent gene expression in actively dividing cells, and the other that controls gene expression in cells ready to exit the cell cycle. Three of these transcription factors – E2F3A, E2F, and E2F4– coordinate to control cell division, while two others – E2F3 and E2F4 –combine to stop cell division. These results were obtained using a combination of techniques such as tagged-E2F knock-in mice, cell culture, RNA-sequencing, imaging, and artificial intelligence.

Thanks to the immense power of artificial intelligence, the researchers were able to quantify transcription factors across numerous cells in mouse tissues with a precision that was previously unachievable. "To be able to develop the tools that can detect the infrequent presence of transcription factors in every cell and quantify them is both clinically and biologically relevant," – says co-author, Thierry Pecot, Ph.D. The use of deep learning to quantify transcription factors is a major highlight of the study. Deep learning is a machine-learning technique where computers learn from examples. Deep learning is used in driverless cars to recognize and distinguish objects on the street or in voice control of electronic devices such as smartphones. Using deep learning, the authors were able to analyze proteins in complex tissues, a feat previously thought to be impossible.

A tissue-independent, universal mechanism for cell cycle regulation

Surprisingly, the two E2F transcriptional modules function similarly in all tissue types suggesting a universal mechanism to control cell division in mammals. The authors presented evidence collected via single-cell-level in vivo analysis suggesting that levels of these transcription factors go up and down in dividing cells of all mouse tissues analyzed. This points in the direction of a universal, physiologically relevant model of how E2Fs are expressed and function in mammals.



Future directions

This study provides new insights into how cells regulate division. The authors discovered ‘when and where’ certain key regulators of cell cycle – the E2F transcription factors – are expressed and how it is relevant for coordinating cell-cycle during mammalian development. The study also suggests a universal mechanism for cell cycle regulation.

“The study prompts important questions for future research. We uncovered when and where the on and off switch modules for cell division are expressed in intact organisms. However, we do not know why there are multiple on and off switches, and whether these switches have redundant roles." – Dr. Leone

This study reinforces our current scientific methodology of studying complex biological pathways involved in diseases such as cancer. Model organisms and in vitro studies using cell culture techniques combined with in vivo studies in mammalian models lay the foundation for drug development.

(Reference)

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