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.
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 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.

(Reference)

https://www.phchd.com/global/biomedical