The cell cycle is a highly regulated process that ensures the accurate replication of genetic information and the transmission of the cellular state from one generation of cells to the next. Pluripotent stem cells (PSCs) exhibit a robust yet flexible identity, maintaining an efficient self-renewing state with a fast cell cycle while responding to external cues that induce cell differentiation. This response is notably heterogeneous, resulting in an asynchronous and inefficient differentiation process in vitro. Previous evidence indicates that the activation of cell-type-specific genes is restricted to the G1 phase, which lengthens during differentiation. This suggests a fundamental link between cell-cycle regulation, pluripotency, and cell differentiation. However, the key regulators and epigenetic mechanisms underlying this interplay are not yet well understood.

To address this question, we have developed a novel approach to study gene expression and chromatin accessibility dynamics during the cell cycle. We combined high-depth single-cell multiome sequencing, biophysical modeling, and advanced deep learning techniques. First, we used a novel deep learning tool that assigns a cell cycle phase to every cell based on their spliced and unspliced mRNA levels. We then developed a biophysical model that describes the dynamics of gene-specific mRNA transcription, nuclear retention, and degradation rates during the cell cycle. Finally, we quantified the chromatin accessibility dynamics during the cell cycle at high temporal resolution and identified the cell-cycle dependent activities of transcription factors (TFs). This allowed us to uncover key TFs coordinating the cell-cycle regulation some of them known pluripotency factors, highlighting the link between cell cycle and pluripotency maintenance. Overall, we believe that our novel approach will open the possibility to shed new light on the interplay between pluripotency maintenance, cell differentiation and the cell cycle.

**Date:** Monday, December 4, 2023  
**Time:** 15:30h - 16:45h  
**Location:** U1.193, Biozentrum  
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