

**GRADUATE SCHOOL OF BIOMEDICAL SCIENCES**

**CANCER BIOLOGY PROGRAM**

**Ph.D. THESIS DEFENSE**

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The Role of S-phase Speed During an Erythroid Transcriptional Switch

The cell division cycles of differentiating cells are coordinated so as to generate sufficient numbers of mature cells. The cell cycle may also regulate the process of differentiation, in ways that are not well understood. We previously discovered that during erythropoiesis, the cell cycle is synchronized with a specific developmental switch, where erythroid progenitors known as colony-forming-unit-erythroid (CFU-e) transition from a self-renewal state to a state of erythroid terminal differentiation (ETD). This switch takes place during a single cell cycle S phase and is dependent on S-phase progression. My work shows that this S phase is unusual, in that it is shorter than S phase in preceding cycles, as a result of a global increase in replication fork speed. I found that the CDK inhibitor, p57KIP2, negatively regulates replication fork speed in self-renewing CFU-e, and its down-regulation at the switch to ETD results in S-phase shortening. p57KIP2-mediated inhibition of CDK2 is essential for CFU-e self-renewal. It exerts this effect by reducing replication stress and also reducing the probability of transition from CFU-e to ETD, promoting CFU-e self-renewal instead. CDK2 inhibiting drugs that mimic the action of p57KIP2 stimulate erythropoiesis both in vitro and in vivo, through expansion of the CFU-e pool. In addition to p57KIP2, E2f4 also regulates S-phase shortening and the efficiency of the CFU-e to ETD transition. Overall, my work shows that S-phase speed regulates a key erythroid cell fate decision, and suggests a possible translational application of CDK2 inhibiting drugs in the stimulation of erythropoiesis.

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