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Review

Linking the Cell Cycle to Cell Fate Decisions

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Pluripotent stem cells (PSCs) retain the ability to differentiate into a wide range of cell types while undergoing self-renewal. They also exhibit an unusual mode of cell cycle regulation, reflected by a cell cycle structure where G1 and G2 phases are truncated. When individual PSCs are exposed to specification cues, they activate developmental programs and remodel the cell cycle so that the length of G1 and overall cell division times increase. The response of individual stem cells to pro-differentiation signals is strikingly heterogeneous, resulting in asynchronous differentiation. Recent evidence indicates that this phenomenon is due to cell cycle-dependent mechanisms that restrict the initial activation of developmental genes to the G1 phase. This suggests a broad biological mechanism where multipotent cells are 'primed' to initiate cell fate decisions during their transition through G1. Here, I discuss mechanisms underpinning the commitment towards the differentiated state and its relation to the cell cycle.

Trends

Pluripotent and neural stem cells have a short G1 cell cycle phase. Committed cells extend their G1 phase and cell cycle length.

Stem cells initiate fate decisions by activating developmental genes in G1 phase. In pluripotent stem cells, developmental genes are cell cycle regulated and respond to extracellular differentiation cues in G1.

Developmental signaling pathways connect to target genes in G1 phase, allowing for activation of transcriptional programs that direct cell fate.

Cyclin-dependent protein kinases (CDKs) control the activation of developmental genes in G1. CDKs target transcription factors, such as SMAD Family Member (SMAD) 2,3.

The epigenetic landscape changes at developmental genes in G1. This is likely to be important for initiation of developmental programs.

Individual Stem Cells Respond to Differentiation Cues with Asynchronous Kinetics

When PSCs are exposed to differentiation-inducing signals, individual cells activate developmental pathways with asynchronous kinetics (Figure 1A). Although this phenomenon applies to all multipotent cells, an understanding of this phenomenon at the molecular level has been elusive. One anecdotal explanation for this observation has been that local differences in cell density create variations in factor concentrations that, in turn, support differentiation and self-renewal to varying degrees. However, recent work now indicates that asynchronous differentiation and initiation of cell fate commitment is linked to the cell cycle. The central observation driving this concept is that G1 cells respond to specification signals more rapidly than do cells at other cell cycle positions. This confers the ability of G1 cells to activate differentiation programs almost immediately following stimulation [1–3] and manifests in S-, G2-, and M-phase cells, activating differentiation programs with delayed kinetics. This delay is directly related to the time taken to transition into G1 phase, when developmental programs are activated. The model predicting this has been confirmed with the Fluorescence Ubiquitin Cell Cycle Indicator (Fucci) system [2], using the kinetics of developmental gene activation as a read-out (Figure 1B). The molecular mechanism controlling phase-specific cell fate commitment is not completely resolved and is a major focus of this review (see Outstanding Questions).

The idea that cells initiate fate decisions in G1 phase is not a new concept. For example, cells make the decision to cycle or withdraw from the cell cycle during every round of cell division by a mechanism known as 'restriction point' (R-point) control [4]. The R-point serves as a molecular switch that controls cellular 'decisions' relating to continued division or entry into the quiescent state (Go). This pathway involves the integration of extracellular mitogenic signals with the cell cycle machinery, converging on cyclin-dependent kinase (CDK) activity, the retinoblastoma protein (RB) family, and E2F target genes [5]. Other examples where cell fate decisions are coupled to G1 transition include mating type switching in budding yeast [6], the replication origin

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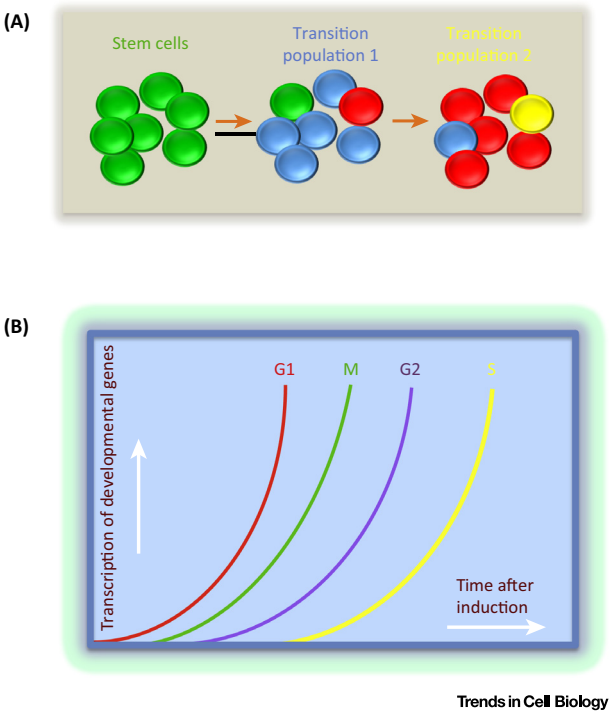

Figure 1. Initiation of the Differentiation Program in Pluripotent Stem Cells Is Coupled to Cell Cycle Progression. (A) Stem cells exposed to cell fate-specification cues differentiate as an asynchronous wave. (B) The asynchronous differentiation program can be accounted for by the activation of developmental genes in G1 phase of the cell cycle. Cells in G1 respond rapidly to differentiation cues, whereas cells in S, G2, and M phase experience a delay, indicated by the kinetics of transcriptional activation.

decision point [7], and size control mechanisms [8]. In most of these cases, the general theme is that extracellular signals activate signaling pathways within the cell, resulting in the coupling of cell cycle-dependent transcriptional responses to cell fate decisions.

Why should cells preferentially make cell fate decisions from G1 phase and not other cell cycle phases (see Outstanding Questions)? Although speculative, it is feasible that transcriptional programs linked to cell identity can be rapidly reset following exit from M phase. The transition from M phase to G1 is associated with dramatic changes in nuclear architecture [9], including reformation of the nuclear envelope, chromosome decondensation and extensive chromosome repositioning in 3D space [10,11]. In the presence of pro-differentiation signals, G1 phase would potentially establish a favorable epigenetic and nuclear architectural environment that allows developmental programs to be activated (Figure 2). This general idea is supported by numerous observations. For example, the potential for a gene to be activated following M phase is dependent on its relocalization to the nuclear periphery in G1 [12]. In the context of cell fate decisions, lineage-specific genes would be reorganized and recruited to the nuclear lamina by a mechanism dependent on the temporal signaling environment. This is likely to be associated with the dynamic nature of chromatin organization in early G1 cells and its continued refinement during the transition to S phase [13]. This is consistent with observations that topologically associating domains (TADs) and promoter-enhancer loops are established in G1 [14]. In this scenario, cell fate specification signals and the cell cycle machinery would act on permissive chromatin in G1 to elicit cell fate decisions.

These observations point towards a set of general principles that make G1 phase special with regards to cell fate choice (Figure 2). First, they indicate that G1 represents a permissive phase for initiating cell fate decisions through control of 'decision' genes at the transcriptional level. Second, they indicate that cells are unresponsive to inductive cues outside of the G1 phase. Mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK), phosphoinositide