Reprogramming of cellular identity is fundamentally at odds with replication of the genome: cell fate reprogramming requires complex multidimensional epigenomic changes, whereas genome replication demands fidelity. In this review, we discuss how the pace of the genome’s replication and cell cycle influences the way daughter cells take on their identity. We highlight several biochemical processes that are pertinent to cell fate control, whose propagation into the daughter cells should be governed by more complex mechanisms than simple templated replication. With this mindset, we summarize multiple scenarios where rapid cell cycle could interfere with cell fate copying and promote cell fate reprogramming. Prominent examples of cell fate regulation by specific cell cycle phases are also discussed. Overall, there is much to be learned regarding the relationship between cell fate reprogramming and cell cycle control. Harnessing cell cycle dynamics could greatly facilitate the derivation of desired cell types.

Keywords: cell cycle speed; cell fate; hematopoietic progenitors; pluripotent stem cells

Abbreviations
CDKs, cyclin-dependent kinases; cLADs, constitutive LADs; fLADs, facultative LADs; GMP, granulocyte-monocyte progenitors; h/mESCs, human and mouse embryonic stem cells; iPSCs, induced pluripotent stem cells; LADs, lamin-associated domains; MBT, midblastula transition; MKL1/SRF, megakaryoblastic leukemia-1/serum response factor; PRC2, polycomb repressive complex 2; PTMs, post-translational modifications.
with divergent fate commitment [11]. Similarly, S-phase length is generally constrained but its shortening is seen in erythroid differentiation and neural progenitor commitment [12,13]. Below, we will first discuss how overall cell cycle speed may impact cell fate decisions without discriminating the specific mode of cell cycle length modulation. We then lay out prominent examples where the regulation of particular cell cycle phases is implicated. Potential future research directions are discussed at the end.

**Cell cycle speed varies in many cellular contexts**

One of the most striking cell fate transitions is exemplified by Yamanaka reprogramming, where the four transcription factors Oct4, Sox2, Klf4, and c-Myc can turn somatic cells into pluripotent stem cells (iPSCs) [14]. Fast cell cycle promotes somatic cell fate transition into pluripotency [15]. This cell cycle-facilitated fate transition is echoed by differentiating tissue stem cells in vivo, where differentiation is often accompanied by a period of rapid proliferation [16]. How cell cycle dynamics impart specific cell fate choices during lineage specification continues to be an active area of research [13,17,18]. Cells of the hematopoietic system, for example, display extensive heterogeneity in cell cycle dynamics [19]. Hematopoietic stem cells are predominantly quiescent, and their differentiation is accompanied by cell cycle remodeling and acceleration, reaching peak proliferation as lineage-committed progenitors. The heterogeneity in cell cycle dynamics is necessary to maintain tissue homeostasis [20], with each cell type showing characteristic cell cycle behavior. Disruption of the stereotypic cell cycle behaviors occurs during aging and alters the clonal composition that collectively comprises a tissue. While this phenomenon was first described for the hematopoietic tissue in the form of clonal hematopoiesis [21], similar observations have been made in other tissues [22]. As more detailed studies on the cell cycle dynamics of the expanded clones continue to emerge, a significant contribution by these clones to aging and age-related diseases, such as cancer, is highly anticipated. Thus, understanding the mechanisms of cell fate regulation by cell cycle dynamics is of fundamental as well as clinical importance.

**Challenges associated with copying the complex epigenome**

The linear genome is copied by DNA polymerases following Watson–Crick base pairing. Copying the epigenome, however, requires many other types of molecules, as well as their associated modifications or partner molecules. These include, among others, histone post-translational modifications (PTMs), interactions between sequence-specific transcription factors and chromatin, as well as proper chromatin compartmentalization such as chromatin–lamina interactions. For cellular identity to faithfully propagate across cell generations, all aspects pertinent to epigenome maintenance have to be accurately reinstated after each mitosis. Reduced fidelity in each of these aspects could offer opportunities for cell fate change, as occurs during normal development or diseases such as malignancy.

**Achieving proper activity of epigenetic enzymes**

Certain epigenetic enzymes are directly regulated by cyclin and cyclin-dependent kinases (CDKs) [4]. The catalytic subunit of the polycomb repressive complex 2 (PRC2), EZH2, is responsible for depositing histone H3 lysine27 trimethylation (H3K27me3) to suppress target gene expression. Thr350 of EZH2 resides in an evolutionarily conserved CDK consensus phosphorylation motif. Thr350 phosphorylation by CDK1 and CDK2 activates EZH2 methyltransferase activity and recruits it to the promoters of its target genes. Some of these targets are lineage-specific genes, such as HOX genes and SOX family members, whose silencing is thought to help maintain stem cell identity [23,24]. Others reported that phosphorylation of EZH2 Thr487 by CDK1 disrupts its binding to other PRC2 components, leading to osteogenic differentiation of human mesenchymal stem cells [25]. Although the exact functional consequence of CDK phosphorylation differed in these reports, possibly related to the different cellular contexts, these studies illustrate that the activity of a prominent histone-modifying enzyme likely oscillates throughout the cell cycle. Therefore, establishment of proper cell identity needs to co-ordinate with cell cycle dynamics to ensure the proper activity, specificity, and/or duration of the epigenetic machineries.

**Mitotic bookmarking**

The condensed mitotic chromatin is thought to be incompatible with active transcription, with most of the general transcription machinery components stripped away [26]. When the daughter cells need to resume transcriptional identity, how is the transcriptional machinery directed back to the proper genomic sites? A process called ‘mitotic bookmarking’ has been proposed [27]. Some sequence-specific transcription factors can remain bound to the mitotic chromatin. For
example, enhancers of stem cell-related genes are book-
marked by pluripotent transcription factors [28,29].
Additionally, histone PTMs might constitute a book-
mark directly, as seen in erythroid cells, where histone
acetylation widely marks mitotic chromatin [30]. In
other instances, global DNA accessibility has been
shown to remain unaltered during mitosis [31,32], and
different classes of genes could employ distinct book-
marking mechanisms. Palozola et al. [33] revealed that
genes involved in general cell growth and rebuilding of
daughter cells are activated before those specifying lin-
eage identity. It is conceivable that corruption of the
marking mechanisms could lead to cell identity
change or crisis, such as cancer. Indeed, the bookmark-
proteins BRD4 has been a prominent target for the
BET inhibitors [34–36].

Reinstating lamin-associated domains
As part of the nucleoskeleton, the nuclear lamina is
localized at the inner nuclear periphery to provide
structural support for the nucleus. Meanwhile, it teth-
ers heterochromatin to the nuclear periphery [37]. The
heterochromatic regions connected to the nuclear lam-
ina, known as lamin-associated domains (LADs), con-
tain relatively few genes and exhibit a repressive
chromatin state [38]. Actively transcribed regions are
spatially associated with nuclear pores or localized in
the nuclear interior [39]. Such spatial organization is
considerably supported by the nuclear lamina, sug-
gesting a significant role for the lamina in genome
organization [40,41]. Lamins are direct targets of
CDKs [42–47], an interaction which results in their
disassembly and solubilization during nuclear envel-
opese breakdown at mitosis [48]. Therefore, resurrecting
the lamina–chromatin association upon nuclear envel-
opese reformation could represent another challenge
following mitotic exit. Using a modified DamID
assay, Kind et al. tracked the fate of LADs, which are
characterized by histone H3 lysine 9 dimethyla-
tion (H3K9me2). They found that upon mitosis,
LAD positioning is stochastically reshuffled rather
than faithfully inherited [49]. This surprising finding
suggests a substantial reorganization of the genome
immediately after mitosis, contrasting the observation
that cell fate is largely preserved after cell division in
most instances. Further studies revealed that LADs
include constitutive LADs (cLADs) and facultative
LADs (fLADs). cLADs are cell-type invariant, while
fLADs only interact with the nuclear lamina in cer-
tain cell types [50–53]. Thus, LAD rearrangements
might be dominated by fLAD reshuffling, constituting
an opportunity for the rewiring of gene expression
programs as cell division progresses. Given the impor-
tance of the nuclear periphery in organizing the gen-
ome in 3D and its obligatory destruction at mitosis in
mammalian cells, reinstating the proper laminar–
chromatin interaction after mitosis represents another
important point of cell fate regulation. Viewed in this
light, progeria mutations in the canonical nuclear
lamina gene, lamin A [54], might interfere with the
whole spectrum of cell fates required for an adult
organism, even though early development could pro-
gress largely normally [55,56].

Fast cycling cells are more permissive for fate transition
Considering the significant challenges in copying the
epigencode, it is perhaps not surprising that frequent
mitoses could direct assaults on cellular identity.
This notion is supported by studies in somatic cell
reprogramming into pluripotency, where rapid cell
cycle greatly promotes cell fate transition into
pluripotency. The original study showed that c-Myc
significantly promotes proliferation and increases
reprogramming efficiency [14]. Subsequent mechanistic
studies, including manipulation of key cell cycle
regulators, confirmed the importance of cell cycle
dynamics for reprogramming. Inhibition of p53/p21
or overexpression of Lin28 can accelerate cell cycle
and promote reprogramming [57–62]. Conversely,
inhibition of Rb or Ink4/Arf, well-known cell cycle
inhibitors, also promotes reprogramming [63,64]. A
direct comparison of human fibroblasts from differ-
ent ages revealed that aged cells reprogram less effi-
ciently than young cells [65]. Since aged cells
upregulate the p53/p21 pathway and tend to undergo
senescence, these results further support that cell
cycle activity is critical for reprogramming fate tran-
sition. In agreement with this model, a molecular
roadmap charted out that strong upregulation of cell
cycle genes accompanies reprogramming [66]. Fur-
thermore, instead of manipulating the cell cycle, sim-
ply isolating fast-cycling cells during reprogramming
can recover most of the reprogramming-permissive
cells [15]. More strikingly, specific hematopoietic pro-
genitors, a subset of the granulocyte-monocyte pro-
genitors that naturally cycle at a speed of ~8 h/cycle,
reprogram in a nonstochastic manner, with almost all of their progeny turning into mature
iPSCs upon Yamanaka factor induction. In these
hematopoietic progenitors, activation of the endoge-
nous pluripotency locus Oct4 could be detected start-
ing as early as ~48 h following factor induction
[15,67], indicating that the barriers demarcating
somatic cells from pluripotency become severely degraded.

**Potential molecular consequences of rapid cell cycle**

Exactly how ultrafast cell cycles subvert the constraints on cell fate are yet to be fully determined, but a few possibilities emerging from recent literature are discussed in the following sections.

**DNA demethylation**

As discussed above, extreme cell cycle acceleration may compromise cells’ ability to faithfully restore the epigenome, providing a window of opportunity for cell fate change. One specific example is DNA CpG methylation, maintenance of which is largely catalyzed by the DNA methyltransferase Dnmt1 [68]. Given that Dnmt1 is a slower processing enzyme as compared to DNA polymerase [69,70], it is reasonable to speculate that cell cycle acceleration could interfere with completion of Dnmt1’s job of copying CpG methylation onto newly replicated DNA, leading to progressive hypomethylation [71]. Consistent with this notion, DNA hypomethylation occurs frequently in cancer cells, which are collectively more proliferative [72–74]. It has been reported that fast cell division could lead to DNA hypomethylation, which predominantly resides in the nuclear lamina-associated, late-replicating regions [75–77]. These regions might gradually become hypomethylated following rounds of rapid cell divisions. Even in normal tissues, DNA hypomethylation in late-replicating regions appears to be correlated with proliferation, as hypomethylation is observed in highly proliferative tissues, such as hematopoietic cells, fibroblasts, and placenta, but not in slowly dividing tissues, such as kidney and lung [77]. In contrast, DNA methylation levels are better maintained throughout cell divisions in the early-replicating regions. In slowly dividing cells, DNA methylation could be maintained or even accumulated in the late-replicating regions. As an extreme example, the methylation state of late-replicating regions in the brain (featured as least proliferative) is higher than that of the early-replicating regions, sharply contrasting the highly proliferative placenta, where the methylation state of late-replicating regions is lower than that of the early-replicating regions [77]. Global DNA hypomethylation driven by cell cycle acceleration is seen in primordial germ cell specification during early embryogenesis [78], where parental imprints and epigenetic marks accrued by the embryo are reset [79].

**Time-limited access to chromatin by epigenetic enzymes**

Similar to the maintenance of DNA methylation, evidence from early embryogenesis suggests that cell cycle speed could exert significant pressure on histone PTMs. *Drosophila* early embryogenesis starts with astoundingly fast cell divisions driven by cyclin/CDK1 [80,81]. This occurs in syncytium, where multiple nuclei share the same cytoplasm and divide synchronously. The first eight embryonic divisions are extremely fast, with the interphase of each division lasting less than four minutes. Cell cycle progressively slows during later cycles. At cycle 14, the embryo enters the midblastula transition (MBT) stage, coinciding with a dramatically slowed cell cycle due to CDK1 degradation. This is the stage when zygotic genes are fully activated and histone modifications stabilized, such that the heterochromatic foci become recognizable. How are the heterochromatic foci established during *Drosophila* early embryogenesis? Seller et al. [82] found that Eggless, the *Drosophila* H3K9 methyltransferase, mediates this process. Specifically, the length of interphase limits the access of Eggless to chromatin, leading to insufficient Eggless activity on the chromatin and failure in heterochromatic foci formation. However, as cell cycle lengths at the MBT stage, the effect of Eggless becomes sufficient to establish and maintain heterochromatic foci [82]. This mechanism supports the hypothesis that cell cycle length could regulate the epigenome by controlling the time available for establishing/maintaining epigenetic marks. It is not clear how such a global mechanism imparts specific cell fate decisions, and how different genomic regions might be differentially impacted by the time-sensitive regulation. The MBT stage also coincides with S-phase lengthening, which could potentially affect cell fate choice by additional mechanisms. Multiple of these mechanisms could be active to co-ordinate cell fate specifications, which is discussed in the following sections.

**Delayed restoration of histone PTMs**

To retain the same cell identity after division, histone PTMs behind the replication fork need to be restored, both positionally and quantitatively. Many histone PTMs can be restored to the prereplication level within one cell cycle [83], possibly due to parent histone recycling that preserves the positional information [84]. However, restoration of certain histone PTMs, such as histone H3 lysine 9 trimethylation (H3K9me3) and H3K27me3, could extend over several cellular
generations. Positional restoration occurs immediately after the replication fork and could occur independent of the enzymatic activities that deposit such PTMs. In contrast, quantitative restoration of histone PTMs may require much longer time. These distinct modes of histone PTM restoration suggest the possibility that cellular identity could become corrupted following several rounds of rapid cell cycles, when the protracted restoration of histone PTM levels is compromised.

Globally altered biomolecular concentrations

Cellular concentration of biomolecules has been shown to be dependent on cell cycle length [85]. In most cases, the apparent effect of mitosis on intracellular biomolecules is to have their quantity reduced by half. Therefore, reduction by cell division instead of degradation could be an effective way to globally reduce the quantity of biomolecules. During Escherichia coli balanced growth, most proteins are not actively degraded, when dilution by cell division becomes a dominant strategy to reduce protein concentration [86,87]. Analysis of 100 proteins in human cancer cells revealed that the abundance of proteins with a long half-life depends on dilution through cell division [88]. Indeed, the concept that stable proteins are preferentially retained in slow-dividing or nondividing cells could be recapitulated by transgenically expressed reporter proteins [89]. These data support the hypothesis that cell cycle length can be opted to control and alter the concentration of molecular species dependent on their inherent half-lives. Long-lived molecules accumulate as cell cycle lengths or slows, but are diluted as cell cycle shortens or accelerates.

In cases where such molecules play important roles in specifying cellular identity, cell cycle speed could profoundly affect cell fate choices. Direct evidence supporting this scenario comes from the study of the transcription factor, PU.1, where high PU.1 level induces macrophage differentiation, while its low level induces B-lymphocyte fate [90–93]. PU.1 is a protein with a long half-life [93]. Developing macrophages increase PU.1 concentration by extending their cell cycle length rather than promoting its protein synthesis. Furthermore, PU.1 can promote cell cycle lengthening, allowing itself to accumulate and drive macrophage differentiation in a positive feedback loop [93,94].

While PU.1 could be unique to hematopoietic lineage specification, similar mechanisms might exist with other transcription factors which regulate cell fate by co-opting cell cycle length. Such a cell cycle length-driven mechanism should not be discriminative and could apply to other classes of intracellular molecules. For example, since microRNAs are generally considered to be stable [95–98], cell cycle acceleration preceding reprogramming could lead to globally reduced microRNAs, thereby facilitating the transition into pluripotency, which is devoid of most microRNAs. Thus, it is reasonable to speculate that during somatic cell reprogramming into iPSCs, reduction in somatic microRNA concentration is one of the consequences of rapid cell cycle that aid cell fate transition.

Heightened chromatin accessibility from a weakened actin cytoskeleton

As indicated by the morphological changes accompanying mitosis, that is, mitotic rounding, the actin cytoskeleton undergoes remodeling throughout the cell cycle. Many cytoskeletal proteins are directly targeted by cyclin/CDKs (reviewed in Ref. [99]). In the fibroblast reprogramming model, dramatic downregulation of the actin cytoskeleton occurs as cells undergo this fate transition [100,101]. The systematic reduction of the actin cytoskeletal network is caused by reduced activity of the transcription factors megakaryoblastic leukemia-1/serum response factor (MKL1/SRF) [101]. Hu et al. demonstrated that low actin cytoskeleton is critical for the maturation of reprogramming fibroblasts. Elevated actin cytoskeleton by sustained MKL1 activity potently restricts nuclear dynamics, reduces chromatin accessibility, and inhibits pluripotency activation, partly through constricting the nuclei via the linker of nucleoskeleton and cytoskeleton complex [101]. This work depicts a novel perspective on how cell cycle could regulate cell fate and demonstrates how a ubiquitous structural network could regulate nuclear dynamics and control cell fate.

Specific cell cycle phases integrating with cell fate determinants

Cell fate regulation often occurs in specific cell cycle phases [5,7,8]. The G1-phase is an important time for deciding whether or not to exit the cell cycle (i.e., the restriction point, R-point) [102]. An additional restriction point was discovered later. This new restriction point occurs in the G2/M phase of the preceding cell cycle, yielding different CDK2 levels after mitosis. During G1 phase of the ensuing cell cycle, cells that have inherited higher CDK2 commit immediately to the next cell cycle while those with low CDK2 enter a transient state of quiescence [103]. Such divergent behavior could be traced even further upstream to the S-phase of the preceding cell cycle, when CDK2 was downregulated by DNA damage response incurred.
during replication [104]. These studies indicate that the basic decisions for whether/when to divide again is regulated at specific cell cycle phases [5,7,8], suggesting the importance of molecular events during distinct cell cycle phases.

**G1-phase in pluripotent stem cells**

Both human and mouse embryonic stem cells (h/mESCs) display rapid cell cycle with a distinctively short G1-phase, a topic thoroughly covered in recent reviews [5,105,106]. This unique cell cycle structure is accompanied by unusual expression patterns of the cell cycle machinery, with some differences between human and mouse EScs [5]. High levels of cyclin E, A, B [107–109] and CDK1/2 activity persist throughout the mESC cell cycle [106,108,110], while the expression of the KIP/CIP inhibitors is not detectable [108,110]. Rapid replication fork licensing during G1/S transition by Cdt1 is another important feature reported in hESCs [111]. The pluripotent cell cycle also depends on pluripotency transcription factors, such as Nanog and Oct4 [112,113], as well as on pluripotency micro-RNAs [114]. Therefore, the unique cell cycle machinery is an integral aspect of the pluripotency circuitry.

A short G1-phase is postulated to be important for pluripotency maintenance. Genetic ablation of all cyclin Ds and cyclin Es compromises pluripotency in mESCs [115,116], suggesting G1 cyclins are required for pluripotency maintenance. Notably, G1 cycline–CDKs were shown to stabilize the core pluripotency factors Oct4, Sox2, and Nanog through direct phosphorylation [115], and hyperphosphorylated Rb derepresses Oct4 and Sox2 [64]. Furthermore, EScs of both human and mouse display higher sensitivity to differentiation cues in G1 as compared to when they are in S- or G2-phase [117–119]. Experimentally extending G1-phase in hESCs increases their differentiation potential toward all three germ lineages [120]. Further mechanistic insights were obtained with the help of the FUCCI reporter, a powerful tool for dissecting phenotypes related to cell cycle phases without additional perturbations [121]. hESCs in early G1-phase show higher propensity to differentiate into endoderm and mesoderm, while they tend toward ectoderm when in late G1 [122]. Cyclin D level is low in early G1, allowing Smad2/3 to activate endodermal genes. Sufficient cyclin D1 accumulates in late G1 to complex with CDK4/6, which phosphorylates and inactivates Smad2/3, thereby preventing endoderm fate and allowing neuroectoderm fate [122]. Besides modulating Smad2/3 activity, cyclin Ds can complex with locus-specific transcription factors, recruiting transcriptional coactivators onto neuroectoderm genes and corepressors onto endoderm genes [123]. These studies illustrate how molecular events during specific segments of the G1-phase could oppose pluripotency, and how exempting from the G1/S checkpoint favors pluripotency.

Despite the general consensus on short G1-phase being a characteristic feature of ESCs, a few studies challenged the notion that shortened G1 is required for preventing differentiation. For example, overexpression of CDK inhibitors p21 or p27 could elongate G1 without increasing differentiation of mESCs [124]. In addition, mESCs cultured in the 2i/LIF condition also elongate G1, while their pluripotency is not compromised [125]. These examples demonstrate that pluripotency can be compatible with a lengthened G1-phase, although mechanic understandings are needed for how pluripotency is maintained under these conditions. Some insights could be gleaned from a diapause-like state when Myc is inactivated in pluripotent stem cells [126].

**S/G2/M-phase in pluripotency and reprogramming**

The G2/M-phase-associated CDK1 also helps pluripotency. Some of the mechanisms include promoting genome stability [127], elevating the protein level of Lin28, and controlling metabolic glycolysis via the PI3K-Akt pathway [128]. In mESCs, CDK1 dissociates Oct4 from mitotic chromatin in an Aurkb/PP1-dependent manner to prevent chromatin decondensation prior to mitosis [129]. The importance of S/G2/M-phase in regulating cell fate determination is also supported by cell fusion-based reprogramming studies. Embryonic stem cells, embryonic carcinoma, and embryonic germ cell lines can reprogram somatic cells to activate pluripotency via cell fusion [130]. Using centrifugal elutriation, Tsubouchi et al. [131] enriched EScs at specific cell cycle phases, avoiding interfering the pluripotent status of ESCs as caused by drug-induced cell cycle synchronization. With this strategy, they found that ESCs in late S/G2-phase have an enhanced capacity to reprogram lymphocytes and fibroblasts. ESCs at this cell cycle stage can induce the somatic nuclei to undergo a round of precocious DNA synthesis shortly after fusion, potentially providing an opportunity for changes in the somatic epigenome [131]. It remains unknown whether the S/G2 length can influence the reprogramming potential of these late S/G2 ESCs, and whether the overall cell cycle speed can alter the reprogramming capacity of ESCs via cell fusion.
**S-phase shortening in erythropoiesis**

The transcriptional switch demarcating erythroid terminal differentiation in the fetal liver is accompanied by a shortened S-phase and accelerated overall cell cycle. The rapid progression of S-phase is dependent on the downregulation of the CDK inhibitor $p57^{kip2}$. Low $p57^{kip2}$ leads to global increase in replication fork speed, activation of the erythroid master transcriptional regulator GATA-1, as well as formation of DNase I hypersensitive sites and DNA demethylation of these loci [13,132]. It remains to be determined whether S-phase acceleration is the cause or consequence of the transcriptional changes driving terminal erythroid commitment and how replication fork speed integrates with these processes.

With DNA replication being the hallmark S-phase event, speculative connections could be made from other work delineating the roles of genome replication itself in promoting cell fate change. Earlier studies have shown that activation of lineage specifying gene requires DNA replication [133–138], highlighting the importance of S-phase in determining cell fate. Since replication fork progression temporarily disrupts chromatin structure, S-phase could be required for reconfiguration of lineage-specific chromatin loci [139]. Such disruption and reconfiguration process may create an opportunity for cell fate change. However, since terminal erythroid differentiation leads to eventual enucleation, it is possible that erythroid fate is specified with mechanisms unique to this lineage.

**Conclusions and outlook**

As the cell division cycle globally disrupts and reorganizes the molecular content of the cell, it may represent a most effective path for the genome to be interpreted in a different manner as compared to its predecessors. While the linear genome can be faithfully copied through relatively simple biochemical activities, other components that collectively determine how the genome is expressed have far less stringent, or more versatile, propagating mechanisms during genome replication. We propose that it is the multitude and magnitude of the changes caused by the division cycle, especially those occurring in rapid succession, that present cells with unique opportunities to adopt different identities. The accumulating examples of how cell fate decisions are intertwined with cell cycle regulation demand improved methodologies for unveiling cell cycle dynamics and heterogeneity in live cells, *in vivo* and in a noninvasive manner.

The mechanistic insights on how cell cycle dynamics integrate with cell fate control will need to be investigated from multiple angles. For example, how does a cell take in and allocate its bioenergetic resources? How does this strained bioenergetic state, as represented by the Warburg state [140], shape the biochemical substrate pool for chromatin modulation [141,142]? On the chromatin, would the rapidly progressing replication forks collide more frequently with the transcription machineries [143]? What mechanisms could help to alleviate such collisions? When the need of biochemical reactions, such as DNA replication and transcription/splicing, need to be carried out rapidly with high efficiency and high specificity, how could the myriad reactions be co-ordinated in the crowded yet expansive nuclear space?

Although much is to be learned, the mechanistic insights on the connection between cell cycle and cell fate reprogramming could provide practical instructions on a number of fronts. Reprogramming somatic cells into pluripotency, for example, can be greatly facilitated by cell cycle acceleration [15]. Conversely, differentiating pluripotent stem cells into therapeutic cell types could be potentiated by cell cycle deceleration [120]. It will be important to develop more sophisticated cell cycle manipulation approaches, together with the understanding of how specific genomic regions or configurations respond to cell cycle modulation, to more precisely control cell fate. It is also important to explore how cell cycle dynamics impact reprogramming toward less proliferative cell fates. Understanding intrinsic and inherent cell cycle heterogeneity may help in the identification and eradication of certain rare cell states that found catastrophic cell fates, such as malignancy. Perhaps, cancer itself resembles more closely to a cellular state in which the cell cycle is overly rushed, rather than a cell state in which its genome is overly wrong [144].

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