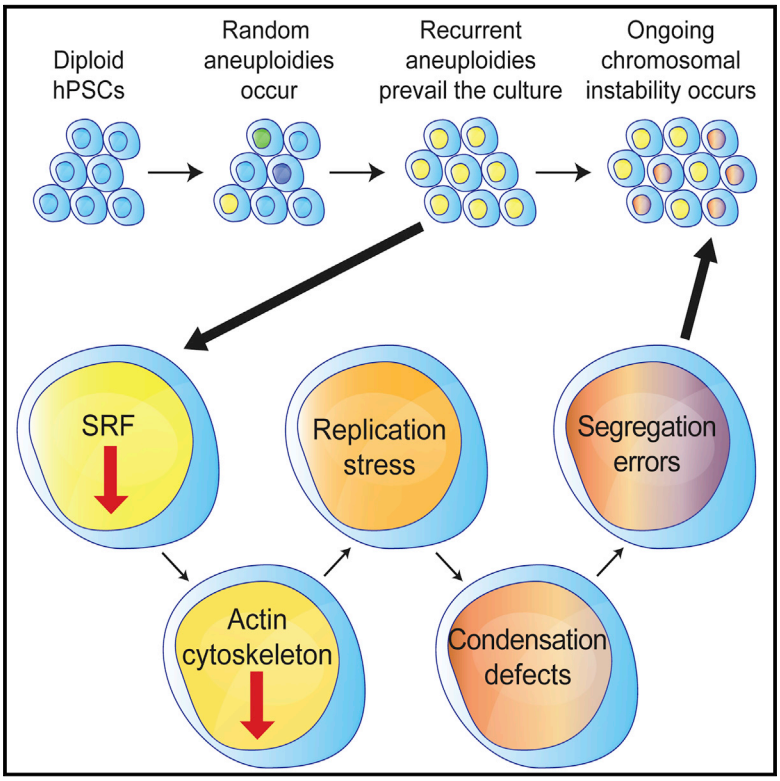
Short Article

Cell Stem Cell

Genomic Instability in Human Pluripotent Stem Cells Arises from Replicative Stress and Chromosome Condensation Defects

Graphical Abstract



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In Brief

Lamm et al. identify a mechanism leading to the ongoing chromosomal instability observed in hPSCs harboring recurrent aneuplodies and which may induce instability in diploid hPSCs. They find that decreased SRF levels cause cytoskeletal impairments that perturb DNA replication and chromosomal condensation, resulting in chromosome segregation errors and genomic instability.

Highlights

- Aneuploid hPSCs exhibit replication stress resulting in condensation defects
- Partially condensed chromosomes lead to segregation errors in aneuploid hPSCs
- Levels of actin genes and their common regulator SRF in aneuploid hPSCs are decreased
- Cytoskeleton impairment perturbs replication and drives ongoing instability

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Genomic Instability in Human Pluripotent Stem Cells Arises from Replicative Stress and Chromosome Condensation Defects

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SUMMARY

Human pluripotent stem cells (hPSCs) frequently acquire chromosomal aberrations such as aneuploidy in culture. These aberrations progressively increase over time and may compromise the properties and clinical utility of the cells. The underlying mechanisms that drive initial genomic instability and its continued progression are largely unknown. Here, we show that aneuploid hPSCs undergo DNA replication stress, resulting in defective chromosome condensation and segregation. Aneuploid hPSCs show altered levels of actin cytoskeletal genes controlled by the transcription factor SRF, and overexpression of SRF rescues impaired chromosome condensation and segregation defects in aneuploid hPSCs. Furthermore, SRF downregulation in diploid hPSCs induces replication stress and perturbed condensation similar to that seen in aneuploid cells. Together, these results suggest that decreased SRF expression induces replicative stress and chromosomal condensation defects that underlie the ongoing chromosomal instability seen in aneuploid hPSCs. A similar mechanism may also operate during initiation of instability in diploid cells.

INTRODUCTION

Human pluripotent stem cells (hPSCs) are commonly used in basic research and hold great promise for regenerative medicine based on their ability to differentiate to every cell type of the human body and their extensive self-renewal capacity. The indefinite self-renewal of hPSCs in vitro enables their prolonged propagation in culture but poses major challenges to their genome stability maintenance (reviewed in Weissbein et al., 2014). hPSCs proliferate fast and have a unique cell-cycle profile as well as aberrant cell-cycle checkpoints (Desmarais et al., 2012; Filion et al., 2009; Weissbein et al., 2014).

During culture propagation, hPSCs tend to acquire both structural and numerical aberrations (reviewed in Lund et al., 2012; Weissbein et al., 2014). Interestingly, numerical chromosomal aberrations in hPSCs tend to result in the acquisition of defined chromosomal aneuploidies. The typical changes are additional copies of chromosomes 12, and 17 X similar to changes found in germ cell tumors (Ben-David et al., 2011; Draper et al., 2004; Mayshar et al., 2010). The rapid proliferation of hPSCs, their inefficient cell-cycle checkpoints (Desmarais et al., 2012; Filion et al., 2009; Weissbein et al., 2014), and their tendency toward centrosomal amplification (Holubcová et al., 2011) suggest that aneuploidy may be actively promoted in these cells by impaired cell division mechanisms. While chromosomal aberrations are presumed to occur randomly, giving rise to karyotypically heterogeneous cultures (Peterson et al., 2008), only a few prevail and eventually take over the culture. Unlike somatic aneuploidies that often lead to altered metabolic properties and defects in cell growth (reviewed in Gordon et al., 2012), aneuploid hPSCs proliferate faster (Ben-David et al., 2014; Werbowetski-Ogilvie et al., 2009), and spend more time in S-phase (Ben-David et al., 2014) than their diploid counterparts. Karyotypic changes of chromosomes 12, and 17 confer hPSCs with a tumorigenic capacity (Baker et al., 2007). Moreover, the most common aberration in hPSCs, trisomy 12, induces profound changes in global gene expression of hPSCs, resulting in increased proliferation rate and tumorigenicity (Ben-David et al., 2014; Yang et al., 2008). Although the chromosomal aberrations that arise in hPSC cultures have been extensively described (Amps et al., 2011; Mayshar et al., 2010), the cellular mechanisms underlying their generation and the tumorigenic potential of hPSCs harboring recurrent aneuploidies remain largely unknown.

Aneuploidy is a hallmark of cancer (reviewed in Gordon et al., 2012). Aneuploidy in cancer can be induced by stress on DNA replication (Burrell et al., 2013). Replication stress is characterized by increased numbers of stalled and collapsed replication forks, leading to DNA damage. One mechanism underlying replication-induced chromosomal instability is the formation of anaphase bridges due to unreplicated or unresolved regions that restrain chromosome segregation by creating a physical link between sister chromatids (reviewed in Ozeri-Galai et al., 2012). In somatic cells, incomplete DNA replication activates checkpoints resulting in prolonged mitotic arrest to enable replication completion and damage repair. However, in hPSCs, incomplete DNA replication fails to generate the single-stranded