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Chromatin and Nuclear Architecture in Stem Cells

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Here we outline the contents of *Stem Cell Reports*' first special issue, on chromatin and nuclear architecture in stem cells. It features both reviews and original research articles, covering emerging topics in nuclear architecture including 3D genome organization in stem cells and early development, membraneless organelles, epigenetics-related therapy, and more.

DNA in living cells is wrapped around a core of histone proteins, which, together with additional structural proteins, comprise the fundamental repeating unit of life, chromatin (Kornberg, 1974). The term "chromatin" was coined in 1882 by Walther Flemming "*for the time being*" to designate "*that substance, in the nucleus, which upon treatment with dyes known as nuclear stains does absorb the dye.*" In other words, Flemming found a novel method to stain structures within the nucleus, and, for a lack of a better word (or understanding of what he was observing at the time), he named it "*the stainable substance of the nucleus*." This coloring technique was the basis of his influential book *Zellsubstanz, Kern und Zelltheilung* (*Cell Substance, Nucleus and Cell Division*) (Flemming, 1882; Paweletz, 2001). In this book he also coined the term "mitosis," and described its various stages in immaculate detail (Figures 1A–1C). Almost 50 years later, in 1929, Emil Heitz, using improved cytological staining techniques that he himself developed, suggested that chromatin is in fact divided into condensed and less active regions largely devoid of genes, which he termed "heterochromatin," and gene-rich domains, which he named "euchromatin" (Figures 1D) (Heitz, 1929). Despite being over-simplistic, these terms are extremely useful, and are extensively used to explain chromatin structure and regulation.

Essentially all cellular processes are governed by changes in chromatin structure, which, in turn, regulate gene expression. Such changes are particularly pertinent in stem cells, which maintain potency but undergo massive changes upon differentiation (Lim and Meshorer, 2020). In recent years, our understanding of chromatin and nuclear architecture has increased considerably, owing to the development of new microscopes and cutting-edge imaging-based methods, breaking the limit of diffraction, and to high-throughput sequencing-based technologies, e.g., Hi-C, designed to capture genome organization in three dimensions. Combined with CRISPR-based techniques, the possibilities become essentially endless, from endogenous labeling of nuclear structures, to CRISPR-based screens for epigenetic and nuclear modifiers, and much more.

This special issue of *Stem Cell Reports*, dedicated to chromatin and nuclear architecture in stem cells, features both original research papers and several review articles, the latter covering chromatin and epigenetic regulation in early mammalian embryogenesis (Xia and Xie, 2020), three-dimensional organization of the pluripotent genome (Pelham-Webb et al., 2020), nucleolar function and organization in pluripotent cells (Gupta and Santoro, 2020), chromatin-associated membraneless organelles in pluripotency (Grosch et al., 2020), and finally, clinical implications of the epigenetic landscape and histone modifications in stem cells (Völker-Albert et al., 2020).

The primary research papers included in this special issue contain method development, where the authors describe a single mammalian locus isolation technique using TALEs (Knaupp et al., 2020), as well as several reports identifying chromatin/epigenetic modifiers regulating pluripotency, stem cell identity, or differentiation. Working with PRC2 mutant mouse embryonic stem cells (ESCs), Perino et al. reveal the functional differences in the recruitment of the PRC2 complexes to chromatin, demonstrating that PRC2.1 recruitment is dependent on MTF2, whereas PRC2.2 recruitment is mediated by PRC1 (Perino et al., 2020). Another study, which focuses on heterochromatin regulation in mouse ESCs, identifies a role for MeCP2 in regulating both chromocenter clustering and the targeting of major satellite transcripts to pericentric heterochromatin (Fioriniello et al., 2020). Vidal et al. show that histone lysine 9 (H3K9) methylation in euchromatic regions, and especially the histone methyltransferase EHMT1, plays essential roles during reprogramming to pluripotency (Vidal et al., 2020). Analyzing the binding partners of a previously identified pluripotency regulator, SET, Harikumar et al. identify the Wnt and p53 pathways as mediators of SET's function in mouse ESCs (Harikumar et al., 2020). Another study explores the regulation of the trophoblast stem cell state by TET1 and 5-hydroxymethylation (Senner et al.2020). Finally, reanalyzing a CRISPR screen

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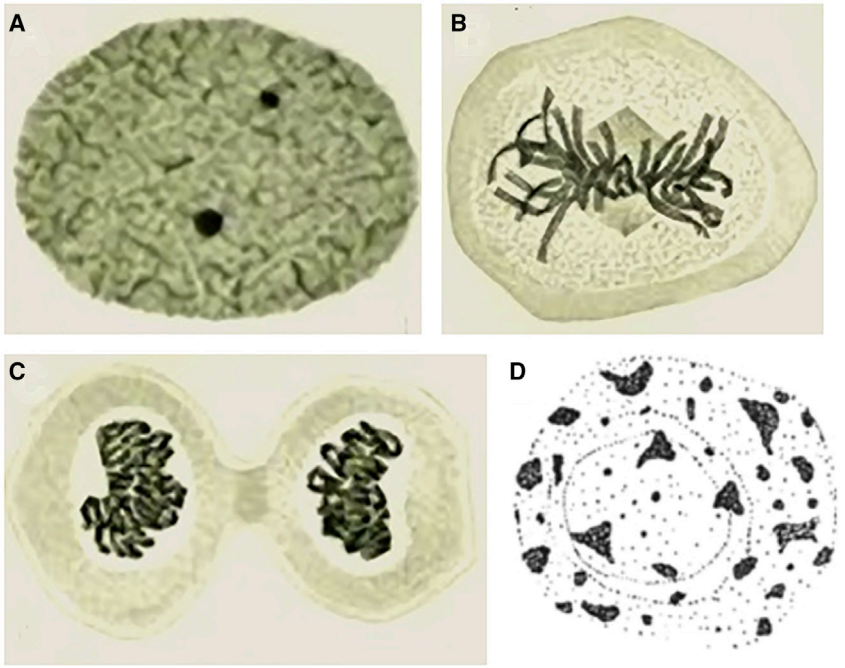

Figure 1. Early Depictions of Chromatin

(A–C) Walther Flemming's drawing of an interphase cell (A), a cell in metaphase (B), and a cell in telophase (C). Images are from Flemming's 1882 book *Cell Substance, Nucleus, and Cell Division*.

(D) Emil Heitz's drawing of condensed heterochromatin domains (black). Image is from his 1929 book *Heterochromatin, Chromocentern, Chromomeren*.

conducted in human ESCs aimed at identifying genes important for ESCs, Lezmi et al. identify the chromatin regulator ZMYM2, which restricts human ESCs growth on the one hand, but is essential for teratoma formation on the other (Lezmi et al., 2020).

This special issue on chromatin and nuclear architecture in stem cells is developed in parallel with an ISSCR digital series on the same topic, which brings together many of the authors from this issue and additional experts in the field for a discussion of these exciting themes. We as guest editors (Figure 2) would like to thank the authors for their contributions to this issue and *Stem Cell Reports* for featuring this important area of research.

Figure 2. Eran Meshorer and Kathrin Plath

Eran Meshorer (left) and Kathrin Plath (right) are the guest editors for this special issue of *Stem Cell Reports*.

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