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Chromatin, nuclear lamins, and maintenance of the differentiated identity

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Abstract

How differentiated cells maintain their identity is a fundamental question in biology. Loss of identity is a hallmark of aged cells and tissues, and is associated with age-related diseases such as neurodegeneration, metabolic disorders and cancer. It is an active process that requires dedicated transcription factor networks. Recent findings suggest that another level of identity regulation involves maintenance of nuclear organization that is unique to the differentiated cell and is dependent on nuclear lamins. Here we review the current understanding of the mechanisms and regulators that maintain the differentiated identity by connecting chromatin state with large-scale organization of the nucleus. We forecast that mechanisms involved in supervising cell identity will be highly relevant to aging biology, cancer, and regenerative medicine.

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Introduction

Long ago, Canard Waddington compared the process of terminal differentiation to that of a ball-rolling downhill into specific valleys of irreversible cell fates [1]. However, over time, the rigid view of "terminally differentiated" cells, was replaced with a more plastic one. For example, nuclear transfer experiments, and forced expression of the myogenic transcription factor MyoD in fibroblasts that resulted in conversion into muscle cells, were among the initial observations demonstrating the fragility of a cell's state [2–5]. More recently, experiments on reprogramming of differentiated cells to induced pluripotent stem cells (iPS), established that the expression of four transcription factors (OKSM: Oct3/4, Klf-4, Sox-2, c-Myc) is sufficient for reverting a differentiated cell into a pluripotent state [6]. Yet reprogramming is an incomplete and inefficient process (see below) indicating that intrinsic barriers exist to maintain identity and prevent re-programming and de-differentiation [7]. As long predicted [8,9], in order for differentiated cells to maintain their identity, both passive and active chromatin-related mechanisms are required. Thus, above "the Waddington valleys" is a "safety-net" that supervises the differentiated identity and prevents the differentiated cells from wandering outside their destination.

Loss of differentiated identity is universal

A central role for supervising identity is attributed to fate-determining transcription factors (TFs) within the fully differentiated cell. For example, Pax5 is required for determination of B-cell fate during development. However, in differentiated mature B-cells, loss of Pax5 resulted in the loss of B-cell identity, trans-differentiation into T-cells, and the development of T-cell lymphomas [10,11]. Indeed, Pax5 is part of a TF network that maintains B-cell identity, and members within this network are highly mutated in lymphomas, suggesting a direct link between an inability to maintain identity and cancer development [12].

A similar scenario takes place in β-cells of the pancreas, which secrete insulin and play a major role in glucose homeostasis. In β-cells, loss of LIM domain-binding protein 1 or the transcription factor Nkx2.2 resulted in loss of β-cell identity and a sharp decline in their ability to perform physiological tasks such as insulin production and secretion [13,14]. Moreover, in type 2 diabetes, a prominent feature is the failure of β-cells predominantly due to glucose toxicity. In this case, loss of β-cell identity is attributed to compromised activity/expression of β-cell transcription factors such as Pdx1, Nkx6, MafA, and Pax6 [15,16].

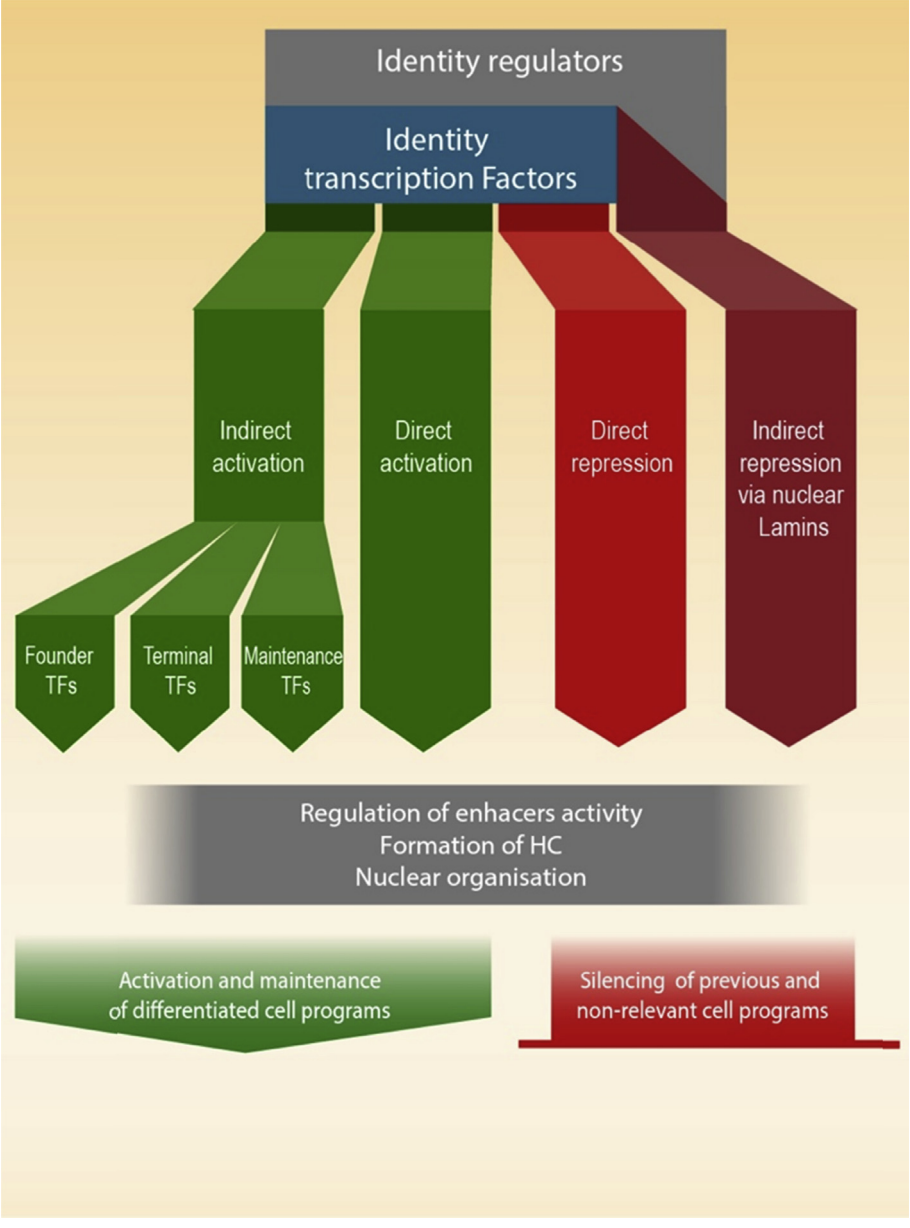
The requirement for identity supervision by transcription factors in various tissues is highly conserved. In the fly testis, the putative TF Chronologically inappropriate morphogenesis (Chinmo) acts to maintain the male identity of somatic cyst stem cells and their progeny, while ectopic expression of Chinmo in ovarian somatic cells is sufficient to induce male identity [17,18]. Likewise, in neuronal tissues an extensive set of transcription factors are required to specify and maintain distinct neuronal identities. For example, homeobox transcription factors such as CEH-43 in *Caenorhabditis*

elegans, Onecut in *Drosophila melanogaster*, and Pax6 in vertebrates are required to establish and maintain the identity of dopaminergic, and olfactory neurons [19–21]. In addition, maintenance TFs, that are required only for maintaining an existing neuronal identity have been described [22]. In other words, TF networks not only establish, but also enforce cellular identities by maintaining the expression of cell-specific gene signatures, and repression of other cell identity programs (Figure 1) [23,24].

Heterochromatin and cell identity

Another level of identity supervision involves the establishment of a nuclear environment that is unique

Figure 1



Maintaining the differentiated identity requires continues supervision. A simplified model for regulation of the differentiated state. Identity regulators act either directly or via identity TFs and maintain the differentiated identity by activating the differentiated transcriptional signatures. Concomitantly they inhibit non-relevant gene programs of previous and non-relevant fates. Identity TFs may activate or repress the above programs. They also induce the expression of fate determining TFs, terminal TFs or maintenance TFs that together with transcriptional co-factors form the identity TF network. In part, maintaining identity programs involves the precise regulation of enhancers. In parallel, a repressive arm of cell identity involves the silencing non-relevant gene programs in the vicinity of LADs. This involves HC inducing modifying enzymes such as H3Kme2/3 methylases, as well as nuclear lamin and other lamina-related proteins. Together they anchor and maintain HC to the nuclear periphery. Both arms of cell identity regulation must be continuously in place to shape the unique nuclear organization of the differentiated cell safeguarding its identity.