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Chemical approaches to cell reprogramming

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Recent advances in cell reprogramming via employing different sets of factors, which allows generation of various cell types that are beyond the downstream developmental lineages from the starting cell type, provide significant opportunities to study fundamental biology and hold enormous promise in regenerative medicine. Small molecules have been identified to enhance and enable reprogramming by regulating various mechanisms, and provide a highly temporal and tunable approach to modulate cellular fate and functions. Here, we review the latest development in cell reprogramming from the perspective of small molecule modulation.

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Introduction

During development and in tissue homeostasis, cell identities are defined by specific gene expression programs, which are governed by core transcription factors. These factors interact with other transcription factors co-occupying specific regulatory elements of target genes to exhibit transcriptional cooperativity. They also recruit other transcriptional co-regulators with chromatin remodeling activities (e.g. epigenetic proteins, such as histone and DNA readers, writers, and erasers) to regulate chromatin accessibility at specific DNA sequences, as well as transcriptional cofactors to activate or repress the activity of transcriptional machinery. These factors collaboratively modulate the frequency, specificity, and strength of gene expression to determine a particular cell fate.

To reprogram and stably establish a cell to a new fate, the balance of the original transcriptional network must be broken. Conventionally, disrupting this balance occurs through genetic approaches, such as overexpressing or knocking down/out core transcription factors. The generation of induced pluripotent stem (iPS) cells by ectopic expression of four transcription factors (iPSC-TFs) exemplifies such approach in this field [1]. Recently, small molecules have proven useful in regulating cell fate and function, especially cellular reprogramming.

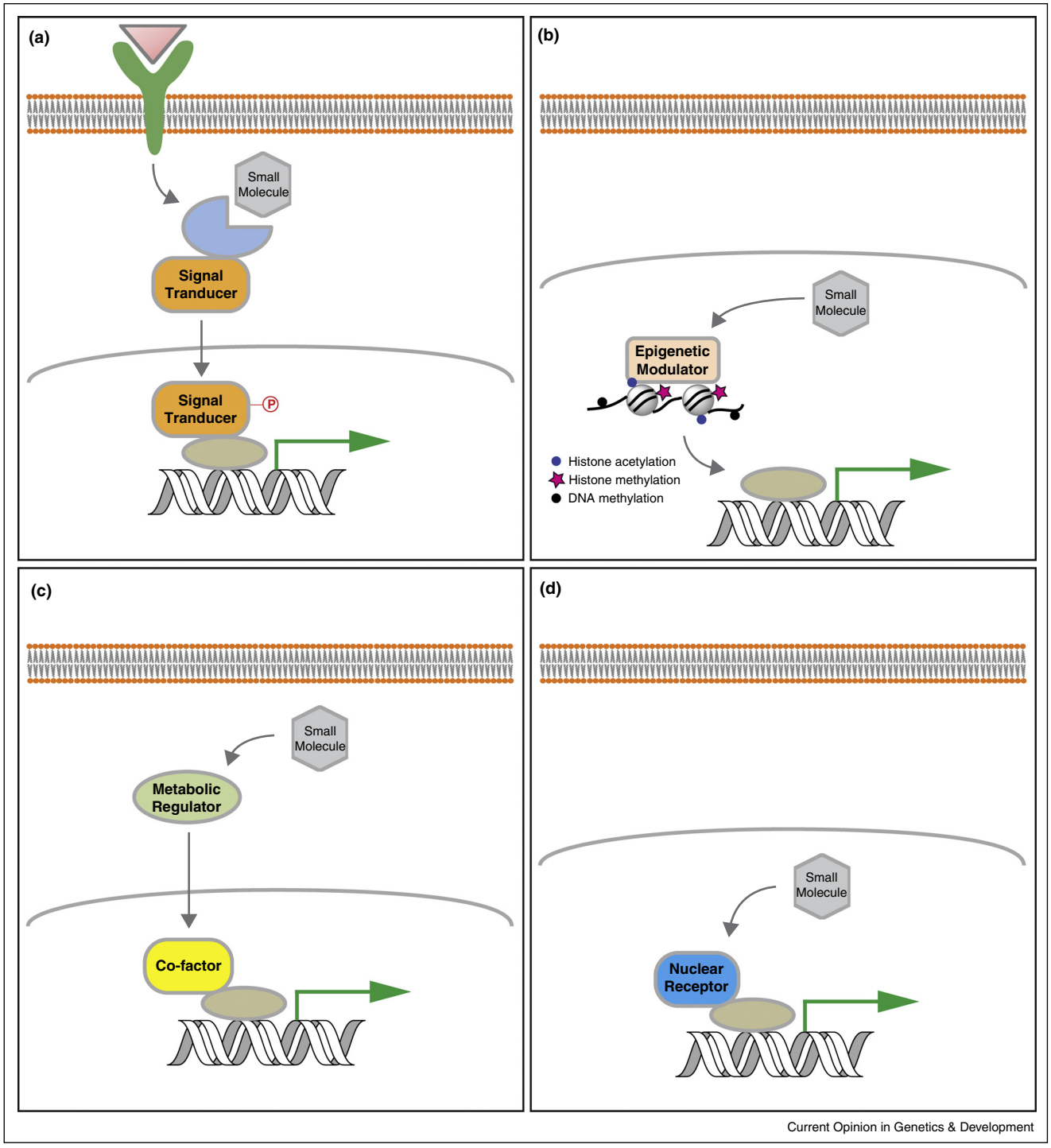
Compared to conventional genetic approaches, small molecules provide several distinct advantages to reprogramming. For example, small molecules modulate specific protein targets rapidly and often reversibly, and thus can regulate cell functions with higher precision in a temporal manner. Additionally, small molecules can be applied at various concentrations and combinations so that their effects are highly tunable. These features can improve their specificity and efficacy, alleviate safety concerns, and potentially overcome hurdles in clinical applications that genetic methods cannot.

Small molecules can regulate gene transcription typically through four classes of mechanisms: signaling pathway modulators, which activate or repress components of signal transduction to regulate downstream transcription activity; modulators of epigenetic proteins, which regulate the activity of epigenetic complexes; metabolic regulators, which adjust cell state and shift balance of metabolites that serve as ligands for proteins (e.g. GPCRs and nuclear receptors) and cofactors for epigenetic proteins; and nuclear receptor agonists and antagonists, which directly modulate transcription by regulating the activity of nuclear receptors (Figure 1). Here, we will review each of these categories for applying small molecules to reprogramming. We will also discuss the transdifferentiation paradigm and its possible mechanisms of action.

Signaling pathway modulators

Signaling pathway modulators represent a major group of small molecules regulating reprogramming. Some signaling pathways directly target the pluripotency transcriptional network to positively affect iPS cell generation. For example, a glycogen synthase kinase (GSK) 3 inhibitor, CHIR99021, was shown to promote maintenance of pluripotency and enhance reprogramming [2–4]. This is consistent with the mechanism that under Wnt stimulation, T-cell factor (TCF), a downstream component of the Wnt pathway could act in an activating complex to bind many pluripotency genes in ES cells, including Oct4, Sox2 and Nanog [5]. The LIF-Stat3 pathway, well characterized to sustain self-renewal of mouse embryonic stem (ES) cells [6], was shown to

Figure 1



Small molecules regulate gene transcription mainly through four classes of mechanisms: signaling pathway modulators, which activate or repress components of signal transduction to regulate downstream transcription activity **(a)**; modulators of epigenetic proteins, which regulate the activity of epigenetic complexes to modify epigenetic marks of certain chromatin region and its gene transcription **(b)**; metabolic regulators, which adjust cell state and shift balance of metabolites that serve as ligands for proteins (e.g. GPCRs and nuclear receptors) and cofactors for epigenetic proteins **(c)**; and nuclear receptor agonists and antagonists, which directly modulate transcription by regulating the activity of nuclear receptors **(d)**.