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Review

Regulation of stimulus-inducible gene expression in myeloid cells

Simona Saccani[a,b,*], Michele Trabucchi[c,**]

[a] Institute for Research in Cancer & Ageing Nice (IRCAN), Equipe Labellisée Ligue Contre le Cancer, INSERM U1081, CNRS UMR 7284, University of Nice-Sophia Antipolis, Faculty of Medicine, 28 Ave de Valombrose, 06107 Nice, France
[b] Max Planck Institute for Immunobiology and Epigenetics (MPI-IE), Stubeweg 51, 7108 Freiburg, Germany
[c] C3M, INSERM UMR 1065, University of Nice Sophia-Antipolis, 151, Route de St-Antoine-de-Ginestière, 06204 Nice, France

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ABSTRACT

One of the best-characterized and biologically important gene expression programmes in myeloid cells is their response to pro-inflammatory stimuli. Macrophages and DCs in particular are key mediators of immune responses, and are widely-used as prototypes to understand and define the determinants of specific and inducible gene expression.

In this review we summarize advances and concepts which have been made towards the understanding of inducible gene expression, with a particular focus on insights gained using the myeloid system as a model. We discuss the emerging concept of layered control of gene regulation and cell identity by different functional classes of transcription factors; and examine recent progress to understanding the molecular processes involved, including the involvement of nucleosome positioning, chromatin modifications, and nuclear architecture. We also address the exciting but less-well understood role of non-coding RNAs in controlling specific gene expression programmes in myeloid and other cell-types.

1. Introduction

Multicellular organisms have evolved mechanisms to allow the establishment and maintenance of cell identity, despite the fact that every cell develops using the same genetic information. Cells of the immune system combine this with the ability to rapidly react and adapt to changes in the environment. In particular, cells of the myeloid lineages, including monocytes, macrophages, and dendritic cells (DCs), respond to a variety of signals ranging from extracellular or intracellular pathogens, tissue damage, and triggering molecules including RNA or DNA, and are able to integrate these to mount an appropriate immune response [1].

Myeloid cells can be induced to express multiple distinct and overlapping subsets of genes with a wide spectrum of biological functions-inflammation, immune response, proliferation and apoptosis [2]. Their responses are selectively governed by different stimuli [2,3] and where the cells are located (*e.g.*, circulating *vs.* tissue resident cells [1,4,5]). Stimulus-driven induction of individual genes is further regulated to enable distinct timings and magnitudes of expression, and together these features present a powerful model system to study the mechanisms controlling stimulus- and cell-type-specific gene expression.

Two distinct layers can contribute to the regulation of gene expression levels. The first-control at the level of transcriptional output – is the focus of this review. The second comprises all post-transcriptional events, such as control of transcript stability and degradation, and translational rate. Although these can also have a major impact on gene expression and hence on cell identity, they will not be covered here.

In this review, we will summarize some of the most important strategies utilized at different levels of transcriptional regulation to control gene expression, with an emphasis on responses to pro-inflammatory stimuli by myeloid cells as model (summarized in Fig. 1). In particular, we will discuss the roles of different classes of transcription factors, both in determining cell lineages and in responding to extracellular stimuli; the role of chromatin and histone modifications in determining the cell-type- and stimulus-specific functions of gene promoters and enhancers; and the role of spatial genomic organization. Further, we will highlight advances made towards understanding the roles of non-coding RNAs (ncRNAs) in the regulation of transcription.

2. Overview: the tool box of transcription regulation

The genomes of eukaryotes are packaged within the nucleus of each cell as chromatin, consisting (at the most basic level) of

* Corresponding author at: Institute for Research in Cancer & Ageing Nice (IRCAN), INSERM U1081, CNRS UMR 7284, University of Nice-Sophia Antipolis, Faculty of Medicine, 28 Ave de Valombrose, 06107 Nice, France. Tel.: +33 493 377 752.
** Corresponding author. Tel.: +33 489 0642 56.
E-mail addresses: Simona.SACCANI@unice.fr (S. Saccani), Michele.TRABUCCHI@unice.fr (M. Trabucchi).

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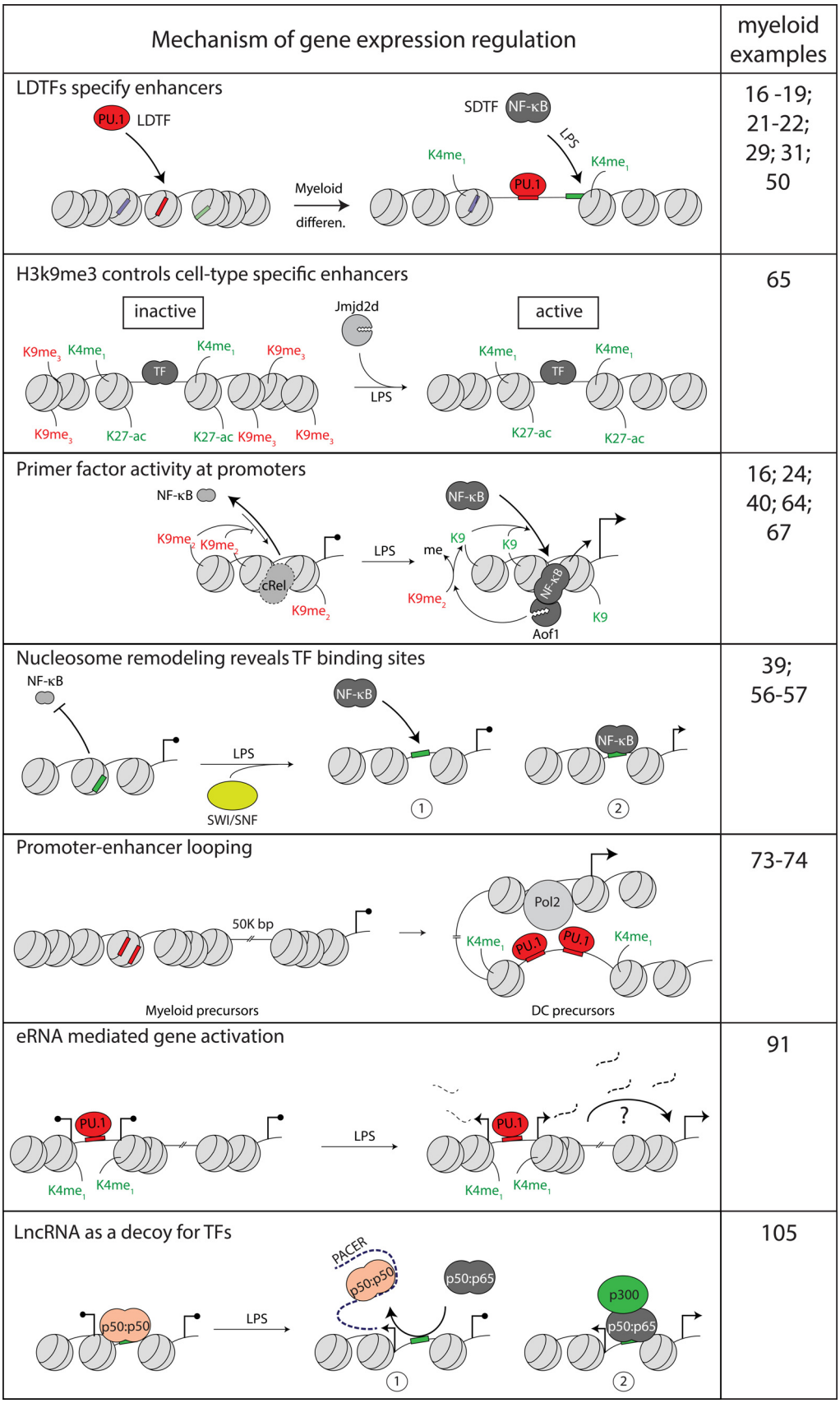

Fig. 1. Mechanisms of gene expression regulation. The different layers of regulation are shown on the left side, and specific examples of their involvement in myeloid gene expression are indicated by the references on the right. Key: red and green boxes on the DNA indicate the DNA binding sites for LDTFs and SDTFs, respectively; post-translational modifications to histone H3 associated with gene activation are indicated in green, those associated with repression are in red; dotted and dashed lines in the lower two panels indicate eRNAs and lncRNA.