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MINI-REVIEW

Dynamics of nuclear receptor target gene regulation

Carsten Carlberg · Sabine Seuter

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Abstract Ligand-regulated nuclear receptors, such as estrogen receptors, glucocorticoid receptor, vitamin D receptor, and peroxisome proliferator-activated receptors, belong to the most widely studied and best understood transcription factors. Therefore, the dynamic nature of transcriptional regulation was observed first with different members of the nuclear receptor superfamily, but is now also extended to other transcription factors, such as nuclear factor κB. Dynamic and in part cyclical processes were observed on the level of translocation into the nucleus, association with genomic binding sites, exchange of co-regulators and chromatin modifiers, occurrence of chromatin marks, and activities of RNA polymerase II resulting in mRNA synthesis. In this review, we summarize recent findings on the dynamic regulation of nuclear receptor target genes in the chromatin context.

Abbreviations

3C	chromosome conformation capture
CDKN1A	cyclin-dependent kinase inhibitor 1A
ChIP	chromatin immunoprecipitation
CoA	co-activator
CoR	co-repressor
ER	estrogen receptor
FRAP	fluorescence recovery after photobleaching
GR	glucocorticoid receptor
HDAC	histone deacetylase
IGFBP3	insulin-like growth factor binding protein
KAT	histone acetyltransferase
KDM	histone demethylase
KMT	histone methyltransferase
Med	mediator
PDK4	pyruvate dehydrogenase kinase 4
PPAR	peroxisome proliferator-activated receptor
qPCR	quantitative real-time PCR
VDR	vitamin D receptor

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C. Carlberg (✉) · S. Seuter
Life Sciences Research Unit, University of Luxembourg,
1511 Luxembourg, Luxembourg
e-mail: carsten.carlberg@uni.lu

C. Carlberg
Department of Biosciences, University of Eastern Finland,
70211 Kuopio, Finland

Introduction

Transcriptional regulation is a central process for nearly all physiological actions of prokaryotes and eukaryotes. In eukaryotes the complex of genomic DNA and nucleosomes, referred to as chromatin, in most cases represses gene transcription (Razin 1998), because it occludes binding sites of DNA-binding proteins. Fundamental decisions in development, such as terminal differentiation of cells, are mediated by a long-lasting programming of chromatin (reviewed in Mohn and Schubeler 2009). However, the epigenetic landscape can also be highly dynamic and lead to short-lived states, such as a response of chromatin to stress signals (reviewed in Talbert and Henikoff 2006). Epigenetic changes origin from reversible post-translational modifications, such as acetylation and methylation, of histone proteins that are directed by histone acetyltransferases (KATs), histone deacetylases (HDACs), histone methyltransferases (KMTs), and histone demethylases (KDMs) associating with DNA-binding transcription

factors (reviewed in Narlikar et al. 2002). The "histone code" consists of specific sets of histone modifications which are associated with genes that are actively transcribed or with those that are repressed (Jenuwein and Allis 2001; Turner 1991). Moreover, plasticity of chromatin is induced by ATP-dependent remodeling complexes, which rearrange the organization of the nucleosomes (reviewed in Hager et al. 2000). These rapid changes in chromatin activation make them permissive for an interference with transcriptional regulation. Most of the dynamic nature of transcriptional regulation was observed at the example of nuclear receptors and their target genes (reviewed in George et al. 2009; Metivier et al. 2006; Trotter and Archer 2007), on which we will focus in this review. However, the principles discussed here may apply to many other if not all eukaryotic transcription factors.

Nuclear receptors

The superfamily of nuclear receptors contains 48 human members, most of which have the special property to be activated by small lipophilic ligands in the size of cholesterol (Nuclear Receptor Committee 1999). Nuclear receptors modulate genes that affect processes as diverse as reproduction, development, inflammation, and general metabolism. The subgroup of endocrine nuclear receptors bind their specific ligands, which are the steroid hormones estradiol, progesterone, testosterone, cortisol, and aldosterol, thyroid hormones or the biologically active forms of the fat-soluble vitamins A and D, all-trans retinoic acid, and 1α,25-dihydroxyvitamin D_3, with a K_d of 1 nM or less (reviewed in Chawla et al. 2001). In contrast, adopted orphan nuclear receptors, such as peroxisome proliferator-activated receptors (PPARs) and liver X receptors, bind to dietary lipids, such as fatty acids and oxysterols, and xenobiotics in the micromolar to millimolar concentration range (reviewed in Mohan and Heyman 2003). Finally, orphan nuclear receptors have no natural ligand and behave like normal transcription factors. The anatomical distribution of nuclear receptors indicates that some receptors have ubiquitous or widespread expression, such as PPARδ, glucocorticoid receptor (GR), and estrogen receptors (ERs), whereas others, such as the vitamin D receptor (VDR) have a more restricted distribution (Bookout et al. 2006).

Recently published chromatin immunoprecipitation (ChIP)-Seq studies reported genome-wide 5.000 to 10.000 binding sites per nuclear receptor (Nielsen et al. 2008; Welboren et al. 2009), while microarrays showed some tenfold less genes being primary target genes within the same cell type (Bunger et al. 2007; Welboren et al. 2009). Interestingly, the majority of these sites are distal to promoters (Carroll et al. 2006), a characteristic probably true for most transcription factors (reviewed in Farnham 2009). This suggests that the regulatory unit of a gene involves multiple transcription factor binding sites at various positions and that the spatial organization of the unit is important to bring via DNA looping at least one activated nuclear receptor protein close to the transcription start site of the respective primary nuclear receptor target gene.

Co-regulators

Nuclear receptors recruit positive and negative co-regulatory proteins, referred to as co-activators (CoAs; reviewed in Aranda and Pascual 2001) and co-repressors (CoRs; reviewed in Burke and Baniahmad 2000), respectively. In a simplified view of nuclear receptor signaling, in the absence of ligand the nuclear receptor interacts with CoR proteins, which in turn associate with HDACs leading to a locally more compact chromatin packaging (reviewed in Xu et al. 1999). The binding of ligand induces the dissociation of CoRs and the association of CoAs (reviewed in Leo and Chen 2000). Some CoAs have KAT activity or are complexed with proteins harboring such activity and this results in the net effect of local chromatin relaxation (reviewed in Glass and Rosenfeld 2000). In a subsequent step, nuclear receptors interact with a member of the mediator (Med) complex, which builds a bridge to the basal transcriptional machinery (Rachez et al. 1999). In this way, ligand-activated nuclear receptors serve first as adaptors between gene regulatory regions and the chromatin modifying enzyme complexes and then as activators of RNA polymerase II.

The switch between gene repression and activation is more complex than a simple alternative recruitment of two different regulatory complexes (Malinen et al. 2008). Most co-regulators are co-expressed in the same cell type at relatively similar levels, which raises the possibility of their concomitant recruitment to a specific promoter. Moreover, it is presently not clear, whether co-regulators already mark in some cases active regulatory elements independent of DNA-binding transcription factors or if they always require active recruitment to target sites. Both aspects emphasize that the spatio-temporal context, i.e., the nuclear organization and the timing of the association of transcription factors and their co-regulators, plays an important role in controlling gene transcription.

Transcriptional dynamics

Most models of transcriptional regulation tend to be static and place transcription factor binding sites into their center.

However, as discussed above, these binding sites and the associated DNA-binding transcription factors provide a platform for highly dynamic events of rapid association and dissociation of co-regulatory proteins. Kinetic descriptions of transcriptional regulation were shown during the last decade preferentially at the example of members of the nuclear receptor superfamily (reviewed in Carlberg 2010). The main techniques used to evaluate transcriptional processes kinetically were ChIP assays, quantitative real-time PCR (qPCR), chromosome conformation capture (3C) assays, fluorescence recovery after photobleaching (FRAP) and real-time, single live-cell imaging of fluorescent-tagged transcription factors (reviewed in Metivier et al. 2006; Stavreva et al. 2009). Please note that the molecular biology methods ChIP, qPCR, and 3C have a resolution of several minutes, whereas the biophysical methods FRAP and live-cell imaging resolve events in the sub-second range. Therefore, both type of methods provide different informations about the duration of a transcription cycle with ChIP, qPCR, and 3C suggesting 30 to 60 min (Degenhardt et al. 2009; Metivier et al. 2003) and FRAP and live-cell imaging indicating far less (reviewed in Hager et al. 2004; Phair et al. 2004). The apparent discrepancy may be explained by the fact that FRAP experiments mainly detect the bulk, rapid, and potentially transient binding of factors, while ChIP assays only detect productive associations of regulatory genomic regions with specific transcription factors. However, presently there are too few studies published in diverse systems, in order to allow a general conclusion.

Using time-resolved ChIP first, Shang et al. (2000) demonstrated that several CoA proteins were recruited in a cyclical fashion to the ER-responding chromatin region of the human trefoil factor 1 (also called *pS2*) gene. However, the master example of time-resolved monitoring of recruitment and release of cohorts of co-regulatory complexes on a single transcription factor binding site was provided by Metivier and colleagues on the same chromatin region (Metivier et al. 2003). The sequential and ordered recruitment of ERα, RNA polymerase II, and many chromatin factors, such as CoAs, CoRs, KATs, HDACs, KMTs, and KDMs, define the direction of cycling. Similar observations were made with the androgen receptor on the human *kallikrein 3* (also called *PSA*) gene (Kang et al. 2002), with the thyroid hormone receptor on the human *dio1* gene (Sharma and Fondell 2002), with VDR on the human genes 24-hydroxylase (Kim et al. 2005; Väisänen et al. 2005), *CDKN1A* (also called *p21*; Saramäki et al. 2009) and insulin-like growth factor binding protein 3 (*IGFBP3;* Malinen et al, unpublished results) and with PPARδ on the human *pyruvate dehydrogenase kinase 4* (*PDK4*) gene (Degenhardt et al. 2009). All these examples show cyclical association of co-regulators and in part also of the respective nuclear receptor with a periodicity of 30 to 60 min. Interestingly, the more recently published reports on *CDKN1A*, *PDK4,* and *IGFBP3* in addition could demonstrate cycling of the synthesis of mature mRNA. Interestingly, periodic limitation of transcription is generated by clearing the chromatin region of transcription factors and by recruiting of HDACs and HMTs. Moreover, the DNA methylation pattern at CpG regions close to regulatory chromatin regions also showed cyclical changes (Metivier et al. 2008). All this induces for a short time a restrictive chromatin environment, which after a few minutes is reversed and a new cycle starts.

Models of transcriptional cycling

In a first simplified analysis, transcriptional cycling depends on stimulus availability, association, and dissociation of the transcription factor and its co-regulators and finally their possible removal through proteasomal degradation. Metivier and colleagues postulate that transcriptionally productive cycles are rather slow, because the initiation of transcription requires specific sequences of events to occur, which are ordered, kinetic, and directional and dependent on productive events that occur frequently from many rapid, stochastic, transient, and unproductive associations of factors (Metivier et al. 2006). In fact, many nuclear proteins rapidly but non-productively associate with regulatory chromatin regions before a deterministic event takes place. Such continuous scanning is essential for transcription and is mirrored in the high mobility seen by FRAP and live-cell imaging.

As an alternative, we recently introduced a model based on stochastic modeling (Degenhardt et al. 2009), in which we assume that at least 30 proteins and six irreversible (i.e., energy consuming) steps participate in each transcription cycle. A recent publication indeed indicated that cycling requires energy consumption (Coulon et al. 2010). In principle, the recruitment and assembly of these complexes could occur in a random fashion, in a partially random fashion (partially determined order) or in a uniquely defined sequential order. In addition, the complexes could be preformed already in the solution of the nucleoplasm or they assemble on the DNA. Based on physiologically relevant protein concentrations, on/off rates, and equilibrium constants, we found that only the models based on sequential or partially determined orders of transcription-complex assembly produce outputs that are consistent with the kinetics of our experimental observations. Per transcription cycle our model distinguishes three phases (Fig. 1): (1) an activation phase in which transcription factors and HATs are recruited to the regulatory regions in order to locally open chromatin, (2) an initiation phase in which Med proteins loop to the RNA polymerase II binding at the

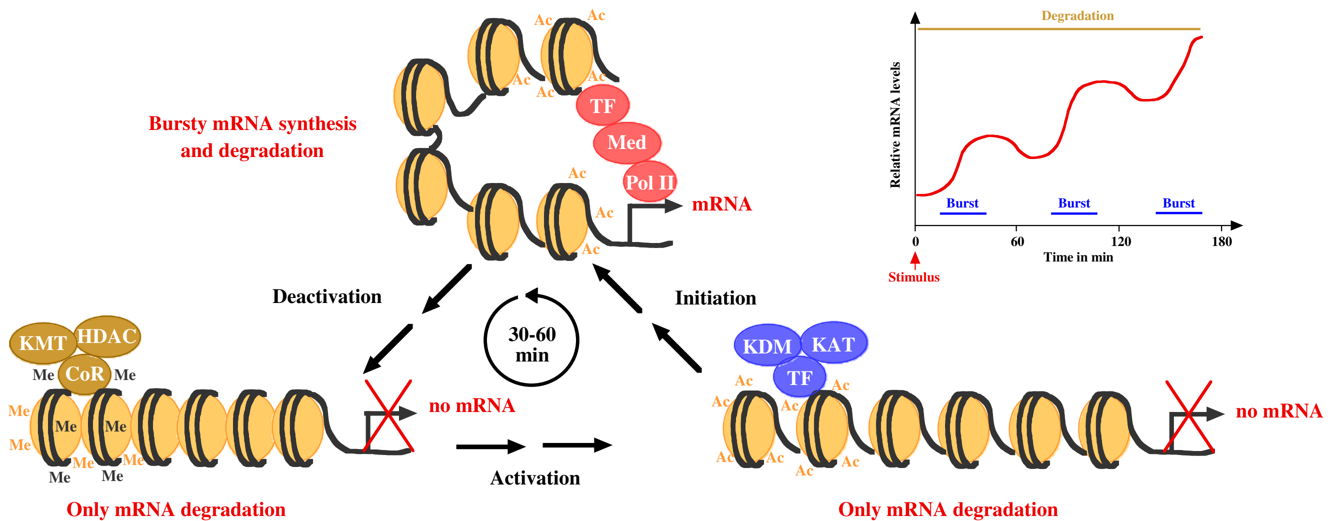

Fig. 1 Model of transcriptional cycling. The model monitors the three phases of transcriptional cycling, of which only the initiation phase results in the synthesis of mRNA, while mRNA degradation occurs at all phases. If a gene shows bursty transcription and the half-life of the mRNA is short enough, this will result in cycling of mRNA levels as schematically depicted in the graph. Please note that only the core proteins of the respective complexes are shown, we assume that each protein complex contains up to 30 components. *Ac*, Acetylated histones; *Me*, methylated DNA (*dark gray*) or histones (*light brown*); *Pol II*, RNA polymerase II; *TF* transcription factor

transcription start site and mRNA transcription starts, and (3) a deactivation phase where HDAC and CoR association lead to chromatin condensation. Hierarchical clustering analysis of the ChIP-association profiles of transcription factors, co-regulators, and chromatin modifications on the *PDK4* gene confirmed this subdivision (Degenhardt et al. 2009). For the cycling of mRNA, the regulatory region of a gene cycles between an active state, during which mRNA is both synthesized and degraded, and an inactive state, during which only mRNA degradation occurs (Fig. 1). Our stochastic transcription model for single cells predicts that on the population level the transcription cycles would fade out 5 h after stimulation, which we confirmed in a long-time course experiment of *PDK4* mRNA accumulation (Degenhardt et al. 2009).

Only bursty genes show cycling on mRNA level

Transcriptional cycling on mRNA level can be observed only, if a gene fulfills two essential conditions: a bursty transcription and a short half-life of the transcript. Therefore, by far, not every gene will show cycling of its mRNA levels. A burst of transcription is in most cases the result of the activation of an inducible transcription factor, such as a member of the nuclear receptor superfamily, having a dominant role on the activation of the respective gene. However, bursty transcription is a quite general phenomenon involving a vast array of mechanisms, such as nuclear translocation and oscillations of second messengers (Ca^{2+}, cAMP; Cai et al. 2008; reviewed in Chubb et al. 2006). The length of the initiation phase influences the size and duration of a transcription burst and is modulated by epigenetic changes of the involved chromatin regions. This suggests that transcription bursts are cell- and gene-specific.

Only when the half-life of the induced mRNA transcript is shorter than the periodicity of the cycling, i.e., in average less than 60 min, there is within one transcription cycle enough mRNA degradation, in order to observe cycling of transcript levels (Fig. 1). This reduces the list of genes that show transcriptional cycling to those that encode short-lived regulatory proteins, such as transcription factors and kinases. Moreover, in order to see transcriptional cycling also on cell population level, cells have to be synchronized in their individual cycles. The stimulation with a nuclear receptor ligand was shown to be sufficient for a population level synchronization of cells (Degenhardt et al. 2009; Saramäki et al. 2009), although in some studies (Metivier et al. 2003; Shang et al. 2000), a pre-treatment with the RNA polymerase II inhibitor α-amanitin was applied.

Why do genes show transcriptional cycling?

The most obvious answer to this question is that transcriptional cycling allows better control of gene transcription. A gene can be silenced far quicker, when it has to confirm every 60 min, if its transcription is still required, than without this control mechanism. The transcription cycle can be stopped in several ways, such as lack of the inducing signal for the transcription factor or changes to the chromatin activation status.

As discussed above, transcription is a dynamic process with high mobility of transcription factors and their co-regulators (Gorski et al. 2006). These proteins contact each other and their specific chromatin binding sites only for a relatively short time (Phair et al. 2004), which provides transcriptional regulation with a stochastic component. This is further extended by the rapidly changing epigenetic state of the involved chromatin regions, as shown for cycling CpG methylation in the regulatory region of the *pS2* gene (Metivier et al. 2008). Could therefore transcriptional cycling be the expression of noisy transcription (reviewed in Hager et al. 2009; Raj and van Oudenaarden 2008)? Positive feedback processes are able to enhance noise, while negative feedback mechanisms in most cases reduce the effect of noise (Thattai and van Oudenaarden 2001). Regular oscillations are a widespread phenomenon in cell biology, including those in glycolysis (Richard et al. 1996), calcium signaling (reviewed in Berridge 1993) and circadian rhythms (reviewed in Carlberg 2000). They show remarkable fidelity and, by this, resistance to noise. Moreover, they are entrained by periodic exposure to signals, but are capable of “free running” without any external signals. In analogy, we assume that the phenomena here described of transcriptional dynamics represent a transcriptional clock, which is entrained by the stimulus of the respective transcription factor, such as a ligand in case of nuclear receptors.

Other forms of transcriptional dynamics

The action of reusable factors, such as transcription factors and their co-regulators, and of the chromatin activation status is intrinsically cyclic, since they act as catalysts or scaffolds. Ensembles of such systems can subsequently display synchronized cycles depending on the stochastic distribution functions of their cycling time. For example, low frequency stimulations of cells with tumor necrosis factor induce cycling of the abundance of the transcription factor nuclear factor κB in the nucleus (Ashall et al. 2009). Moreover, pulsative exposure of cells with ultradian release of cortisol stimulates transcriptional cycling of the nuclear receptor GR (Stavreva et al. 2009). Interestingly, these transcriptional cycles of GR are not observed, when its synthetic ligand dexamethasone is used, which stabilizes the receptor for longer periods than the natural ligand cortisol (Stavreva et al. 2009). We made similar observations when using in constant, i.e., non-pulsative stimulation experiments the potent synthetic VDR agonist Gemini. Gemini failed to induce transcriptional cycling of the human *IGFBP3* gene, while the natural ligand does (Malinen et al, unpublished results). These observations may have implications for the therapeutic application of synthetic nuclear receptor ligands and may explain some of their side effects.

Conclusion

There is no doubt that transcriptional regulation is a dynamic process. However, the impact of the cyclical phenomena here discussed of transcription factor and co-regulator association with regulatory chromatin regions are not fully explored in their impact on transcriptional regulation. In many cases the cycling of nuclear proteins and chromatin activation stages will not translate into a cycling of mRNA or protein levels, i.e., they may not have any direct impact on a physiological function of the cell. Nevertheless, the cycling of transcription factors may represent an important control mechanism, for example in controlling overshooting transcription. Moreover, in attempts to modulate transcriptional regulation, for example in the therapeutic application of nuclear receptor ligands, such as rosiglitazone as PPARγ ligand in the therapy of type 2 diabetes and the ER antagonist tamoxifen against breast cancer, cyclical phenomena should be taken into account since they can have a significant impact on the outcome.

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