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Oct-1, to go or not to go? That is the PolII question☆

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ABSTRACT

The Oct transcription factors recognise an octamer DNA element from which they regulate transcription of specific target genes. Oct-1 is the only member of the subfamily that is ubiquitously expressed and has a wide role in transcriptional control. Through interaction with various partner proteins, Oct-1 can modulate accessibility to the chromatin to recruit the transcription machinery and form the pre-initiation complex. The recruited PolII is induced to initiate transcription and stalled until elongation is triggered on interaction with signalling transcription factors. In this way, Oct-1 can fulfil general roles in transcription by opening the chromatin as well as transduce extracellular signals by relaying activation through various interacting partners. The emerging picture of Oct-1 is that of a complex and versatile transcription factor with fundamental functions in cell homeostasis and signal response in general as well as cell specific contexts. This article is part of a Special Issue entitled: The Oct Transcription Factor Family, edited by Dr. Dean Tantin.

1. Introduction

The characteristic make-up of a cell is determined by its gene expression pattern. The first step in making a protein is the transcription of the DNA into an RNA message which will then be translated, modified and transported to the appropriate location in the cell. Because transcription is the first step in protein synthesis, it is also a major point of regulation.

The appropriate expression of the specific genes required by a defined cell type is determined by chromatin structure which can be more or less permissive for the transcription machinery to access the transcription start site (TSS) of a gene. Transcription by RNA polymerase II (PolII) starts by recruitment of core transcription factors to the promoter to form the pre-initiation complex (PIC). There are also numerous transcription factors that regulate the recruitment and activity of Polymerases. Some of these are general elements of the transcription machinery while others are expressed or activated under precise circumstances to induce expression of specific genes in order to fulfil the requirements of cell function [1]. For a large number of genes, the formation of the PIC is the critical step for transcription and occupancy by the TATA-binding protein (TBP) and PolII directly correlates with transcript accumulation [2]. However, it has become increasingly clear in recent years that many genes, representing as much as 30% of the genome, have a PIC without detectable levels of transcript [2–6]. Genome-wide studies also showed a chromatin structure and histone modifications characteristic of active transcription for this subset of genes [2,3]. These findings introduced PolII pausing as an important transcriptional checkpoint, in which regulation occurs at the stage of elongation rather than recruitment of PolII.

The function of this regulatory mechanism was initially described as a strategy to generate transcripts and protein quickly on demand, as was first described for the Drosophila HSP70 gene [7]. This is consistent with the observation that many of the genes poised for transcription are responsive to stimulus and required rapidly, such as innate immunity [8] and heat shock response [9]. However, experimentally reduced PolII pausing decreases expression of some genes suggesting that the presence of a stalled PolII maintains the promoter 'open' and nucleosome-free to allow access and therefore favour transcription [10]. It has also been proposed that pausing provides means to integrate cellular signals as well as synchronous expression of subsets of genes.

The mechanism of PolII pausing and the machinery that controls the different steps are the focus of intense research but some of the components still remain unclear. The participation of transcription factors (TFs) in the recruitment, activation and pausing of PolII is not yet well understood.

The POU family of transcription factors includes over a dozen proteins that have been implicated in a variety of functions, from the establishment of pluripotency to cell differentiation and homeostasis. Several members are cell-type specific and therefore of limited expression such as Brn-1 [11] in the brain and Oct-2 in neurones [12] and B cells [13]. Other members are expressed at precise times during development such as Oct-4 [14] while Oct-1 is ubiquitous through time and tissue [15]. Though many roles have been attributed to Oct-1, its function

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remains somewhat obscure but its wide distribution suggests it plays a fundamental part in cell homeostasis.

2. The PolII question

The process of transcription consists of three main phases: initiation, elongation and termination. It starts with the recruitment of a hypophosphorylated PolII associated with Mediator to accessible promoters which together with the TATA binding protein complex forms the PIC [16]. This allows PolII to bind the template strand and initiate transcription. The C-terminal domain of PolII is phosphorylated on Serine 5 primarily by the TFIIH-associated kinase Cdk7, which enhances its association with the RNA capping machinery [17]. An early block of transcription at this stage was first demonstrated on the Drosophila HSP70 gene [7] and human myc [18] and since shown to occur genome-wide. The arrest of initiated transcription is mediated by the Negative Elongation Factor (NELF) [19] which interacts with PolII and nascent RNA transcripts through the DRB sensitivity-inducing factor (DSIF) to inhibit elongation [20–23]. More recently, mapping of proteins co-localised with poised PolII identified Gdown1 across the genome [24], which pauses PolII by preventing the TFIIF component of the PIC from binding to elongation complexes. Gdown1 also inhibits the termination factor TTF2, preventing the release of short transcripts and PolII dissociation. Paused PolII is stabilised on many genes by TRIM28 which is also a direct link to the rapid response to cellular signalling [9].

Escape from pausing is facilitated by the kinase activity of the Positive Transcription Elongation Factor b (P-TEFb). This factor consists of cyclin T and Cdk9 which phosphorylates NELF and DSIF causing their release from the PolII complex thus relieving the block of elongation. P-TEFb also phosphorylates the CTD of PolII on Serine 2 which triggers elongation [23,25]. Thus PolII found near the 5′ end of genes is phosphorylated on Serine 5 while the enzyme present downstream throughout the gene, is phosphorylated on serine 2 [17,26]. These modifications of PolII CTD are widely used to determine pausing or processivity throughout the genome.

Though the general mechanism of PolII pausing has been well characterised, the question remains as to how it is directed to specific genes in particular circumstances. Apart from the local chromatin structure that influences recruitment of the basal transcription components [10], the crucial role of proximal promoter features that bear binding sites for TFs in the recruitment and stabilisation of the PIC has also been recognised [27]. The most characterised interphase between PolII and transcription factors is Mediator, a multiprotein complex that functions as a global transcriptional regulator and is considered a general transcription factor [28,29]. Mediator interacts extensively with PolII and also with some transcription factors such as SREBP and VP16 whose binding triggers major conformational changes throughout the complex [30]. In some cases, specific TF-induced structural changes correlate with activation of PolII [31,32]. Mediator binds to hypophosphorylated PolII and has been shown to enhance CTD phosphorylation by the TFIIH Cdk7 [33,34]. This modification disrupts CTD-Mediator binding most likely facilitating the transition from initiation to elongation [35]. In Drosophila, it has been shown that HSF1 stimulates rapid transcription of heat shock genes from a poised PolII through an interaction with Mediator [36,37]. In humans, c-myc is required for self-renewal and proliferation [38] and binds to a high number of active promoters. It was shown that the heterodimer c-myc/max binds P-TEFb to facilitate elongation at c-myc-target genes and downregulation of c-myc causes pausing at normally actively transcribed genes [39]. A genome-wide study identified a core promoter feature in Drosophila common to 25% of stalled genes that facilitates pausing called the Pause Button (PB), which together with GAGA and Initiator (Inr) is a good predictor of pausing [40]. However, in mammals, core promoters are much less defined and elements that may facilitate pausing have not been identified [41]. Instead, the establishment and control of pausing seems to be orchestrated by TFs that interact with the core transcriptional machinery. Some TFs such as Sp1 [18] and CTF, have been implicated in recruiting and stalling PolII while others such as p53 stimulate full transcriptional activity [42] which is consistent with the reported interaction with Mediator [28]. But though some TFs involved in this process are emerging, the immense diversity of regulatory programmes implies there must be a wider set of TFs that control PolII pausing and elongation in a gene-specific manner.

3. Oct-1 the basics

A subset of the POU transcription factors recognises the octamer DNA element ATGCAAAT and variations of it [43]. These Oct transcription factors have a central DNA-binding domain and flanking N- and C-terminal domains that confer their specific activity. The most prominent members of the Oct subfamily are Oct-1, Oct-2 and Oct-4 with well-studied roles in important processes [44–46]. Most of them are synthesised as several isoforms that differ in their N- and C-terminal domains which impacts their function [47,48].

Oct-1 is the only one of these factors that is ubiquitously expressed in most cell types examined [13]. It is constitutively present in the nucleus and is normally bound to the octamer DNA elements that are accessible in a constitutive fashion [46,49,50]. Consistent with this property, Oct-1 has been implicated in basal transcriptional regulation [51]. However, it has also been described to respond to signalling through other inducible transcription factors such as NFκB [52].

These findings imply that Oct-1 has a dual function of keeping expression of some general proteins as well as controlling expression of inducible genes.

4. Will you go or will you stay?

The role of Oct-1 in transcriptional regulation has been described on a number of target genes. Most of these studies show Oct-1 participation by identifying octamer elements in the promoters of target genes and changes in their expression when the cellular levels of Oct-1 are manipulated or the binding sites deleted [53,54]. However, the molecular mechanisms by which Oct-1 exerts its variety of regulatory functions remain largely unknown.

Since its first identification in the 90s, considerable effort was invested into unravelling the precise mode of action of Oct-1. Early on it was recognised that Oct-1 facilitates the recruitment of TBP to promoters through a direct interaction for which the localisation of the octamer binding site in close proximity to the TATA box is crucial [55]. The interaction with TBP was mapped to the POU domain of Oct-1 and mirrored in Oct-2 due to the high homology of the POU domains in these proteins. Both, Oct-1 and Oct-2 support early steps of PIC formation and this is part of the activation mechanism of octamer-containing promoters [56]. In the specific case of Oct-2, the interaction with TBP is not sufficient to stimulate transcription but other general transcription factors, specifically TFIID are necessary [57]. Oct-1 binding to proximal promoter sites is increased and stabilised by TFIIB [58], suggesting a mutual effect of recruitment and stabilisation between the basal transcription factors and Oct-1. The binding of the core complex formed by TBP, TFIID, TFIIA and TFIIB to promoters is the first step for the formation of the PIC, which is completed with the recruitment of PolII, TFIIE and TFIIH (Fig. 1A). The role of Oct-1 in supporting PIC formation was confirmed using chromatin immunoprecipitation (ChIP) which showed that its binding to the promoter coincides with PolII recruitment [46,59,60]. The simultaneous presence of Oct-1 and PolII on promoters was described for specific genes [46,59] but also for wider subsets of genes genome-wide [61].

The PolII recruited to Oct-1-core TFs complexes is phosphorylated primarily on Serine 5 of the CTD indicating that it is engaged in initiation [62] (Fig. 1B). The transcriptional activation of these promoters was confirmed by marks of open chromatin such as H3K4 trimethylation [46]. The activation of PolII initiation of transcription is likely to occur through an interaction with MAT1. Together with CDK7 and cyclin H,