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Review

Pax factors in transcription and epigenetic remodelling

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ABSTRACT

The nine Pax transcription factors that constitute the mammalian family of paired domain (PD) factors play key roles in many developmental processes. As DNA binding transcription factors, they exhibit tremendous variability and complexity in their DNA recognition patterns. This is ascribed to the presence of multiple DNA binding structural domains, namely helix-turn-helix (HTH) domains. The PD contains two HTH subdomains and four of the nine Pax factors have an additional HTH domain, the homeodomain (HD). We now review these diverse DNA binding modalities together with their properties as transcriptional activators and repressors. The action of Pax factors on gene expression is also exerted through recruitment of chromatin remodelling complexes that introduce either activating or repressive chromatin marks. Interestingly, the recent demonstration that Pax7 has pioneer activity, the unique property to "open" chromatin, further underlines the mechanistic versatility and the developmental importance of these factors.

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Contents

1. Introduction

Pax factors exert critical roles in early development as revealed by mouse and human mutations (as discussed in other papers of this series). One unique aspect of the structure of Pax factors is the presence of two DNA binding domains (DBD), the paired (PD) and homeodomain (HD) in a subset of factors and their differential use for target sequence/gene recognition (reviewed in [1]).

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These dual modalities of DNA interactions provide versatility for Pax gene action in the control of diverse developmental programmes. Targeted mutagenesis experiments of one or the other DBD have suggested that each DBD may be more critical for specific developmental roles. This review paper will primarily focus on the structure and function of Pax proteins as transcription factors (TF) and particularly, on molecular mechanisms that may provide versatility and specificity of action towards subsets of gene regulatory networks. Beyond the action of Pax factors as classical DNA binding TFs, the recent demonstration that Pax7 can function as a pioneer TF adds a new dimension to the action of these factors [2]. Pioneer factors can access their target sequence in compacted chromatin and lead to chromatin "opening" [3,4]. The pioneer activity is particularly well suited for the action of master regulatory genes because it can modify entire developmental programmes through remodelling of the chromatin landscape.

2. Multiple DNA binding modalities

The Pax family of TFs is quite conserved in evolution (reviewed in [1]) and the hallmark of these DNA binding proteins is the presence of a PD DBD. This review will focus on mouse and human genes that have been the subject of numerous studies. In mammals, there are nine Pax genes (Fig. 1). These genes fall into four subgroups depending on the presence or absence of two domains: these are in addition to PD, a complete or truncated HD and an octapeptide (OP) motif in the linker region between PD and HD. The OP is related to the engrailed-homology motif that was associated with strong transcriptional repression activity [5]. Pax7 is unique in the family for the presence of a C-terminal 14 amino acids sequence, the OAR (Otp/aristaless/Rax), that is found in over 30 paired-type HD proteins but is still of poorly defined activity [6].

DNA binding by Pax factors can primarily involve either PD or HD but the simplistic model of either DBD being responsible for protein:DNA interaction may not be prevalent. Indeed, DNA binding activity is clearly dependent on interactions between the two DBDs. In addition, the C-terminal region of some Pax proteins interacts with the DBDs to influence DNA binding activity. In accordance with the involvement of PD and/or HD in DNA binding, some target DNA sequences contain either a core PD or a HD recognition motif; also, both motifs are often found in the same target regulatory sequences [2,7–9]. Although the specificity of binding of each Pax protein for individual DNA sequences is not well resolved, the available data indicates that different Pax proteins have distinct binding specificity, in particular when comparing the family subgroups. A large-scale analysis of DNA binding properties for many over-expressed human TFs revealed the core PD and HD motifs [10] but not the subtlety of factor-specific binding provided by ChIPseq as discussed below.

The implication of various Pax protein domains in determining DNA binding specificity, and ultimately activity, is further complicated by the existence of splicing variant isoforms for many Pax proteins (variant list reviewed in Ref. [11]). Some of these variants differ from the canonical form by only a few amino acids or represent truncations: they have been associated with either varying strengths of DNA binding or altered specificity/activity.

2.1. The PD domain and DNA recognition

The PD is a bipartite DNA binding structure composed of two helix-turn-helix (HTH) motifs that resemble bacterial DNA binding proteins [7,12]. These two motifs are separated by a flexible linker. The two DNA interacting subdomains of PD are thus structurally related to the HD. Crystal structures of Drosophila Prd [13], PAX6 [14], and PAX5 [15] together with nuclear magnetic resonance analysis of PAX8 [16] have supported the model of the third helix of these HTH motifs being implicated in sequence-specific interactions. In addition, the N-terminal HTH motif, named PAI subdomain, is preceded by a ß-hairpin that acts as a clamp interacting with the phosphate backbone and minor groove. The flexible linker between the N- terminal (PAI) and C-terminal (RED) subdomains interacts with bases in the minor groove. The N-terminal PAI subdomain, more specifically its 3rd helix, fits directly in the major groove [13] and recognises the essential bases for PD binding specificity, *i.e.* the core motif GTCACGC (Fig. 2). For some Pax proteins, DNA interactions extend beyond this core motif, mostly in 3′, to include sequences that interact with the C-terminal RED subdomain. For example, the Pax6 RED subdomain contacts sequences 6 bp downstream of the divergent core TTCACGC to interact with the sequence TG/TA/CN [7,13]. An elegant *in vivo* study of Pax6 point mutations

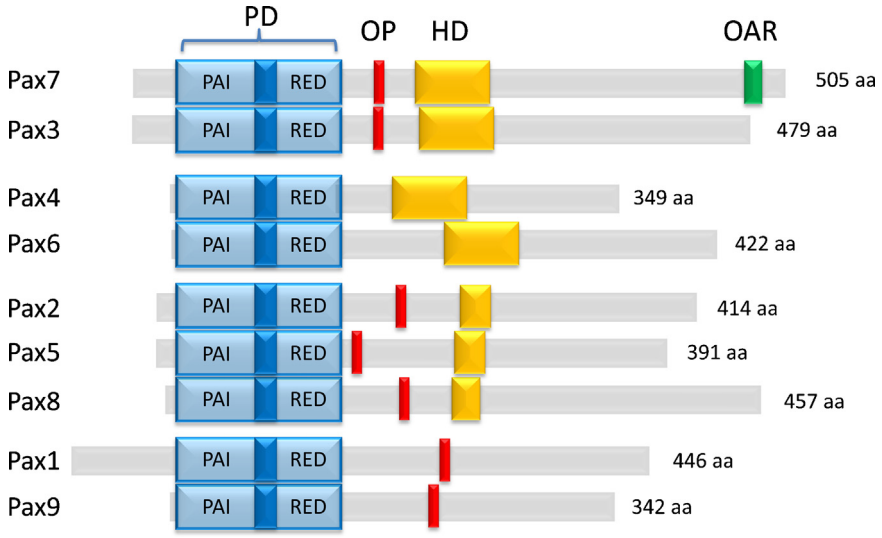

Fig. 1. Structure of Pax transcription factors. Schematic drawings represent the conserved features of the mouse Pax factors. These include the paired (PD) DNA binding domain (blue) present in all Pax factors and subdivided into two helix-turn-helix (HTH) motif (PAI and RED). The Pax family is classified in four groups depending on the presence of other domains such as the homeodomain (HD, yellow, complete in Pax3/7/4/6, partial in Pax2/5/8) and the octapeptide (OP, red, absent in Pax4/6); this domain is homologous to the *engrailed* homology 1 (En1) domains that recruit co-repressors of the Groucho/Tle family. Pax7 is the only member of the family that contains an OAR domain (green) that is also found in many paired-type HD factors.

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