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Review

Promoter elements in endocrine pancreas development and hormone regulation

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Abstract. The research upon the genetics of mammalian endocrine pancreas development gave rise to the detection of several genes that mediate decisions between different cell lineages that finally lead to four different hormone-producing cell types. Transcription factors such as *Pdx1*, *Hnf6*, *ngn3*, *NeuroD/BETA2*, *Pax6* or *Pax4* act within regulatory cascades and networks of transcriptional regulations that provide the genetic background for endocrine pancreas development. In adult animals the anatomical unit of the endocrine organ, the Islets of Langerhans, is built out of α, β, δ and PP cells producing the peptide hormones glucagaon, insulin, somatostatin and pancreatic polypeptide, respectively. Numerous promoter analyses of genes expressed in endocrine cells during development and adulthood have been performed. It turns out that the sequences of cis-regulatory elements within promoters of both, developmental control genes and peptide hormones, can show significant similarities. The relevance of such elements has been demonstrated by several deletion experiments and protein-DNA interaction assays. This review summarizes the currently known cis-regulatory elements that are important for islet development and provides the opportunity of detecting further pancreatic genes by discussing common promoter structures.

Key words. Pancreas; gene regulation; promoters; endocrine development; Islets of Langerhans; glucagon; insulin; β cells; α cells.

Introduction

The development of individual organisms is based on genetic regulation and interaction. The underlying genetic process, namely the control of gene activity, begins with the very first step of gene expression, transcription of DNA. Accordingly, influencing the activity of the responsible enzyme, RNA polymerase II and its cofactors, evolved as a critical mechanism in gene regulation. Thus tight control of the genetic network underlying ontogenesis, and gene-regulated formation of complex organs and structures was established throughout evolution. One example of such a structure are the pancreatic Islets of Langerhans, which represent the endocrine subunit of a complex organ [1–3].

The main compartment of the pancreas is exocrine tissue. It is anatomically organized as acini that produce digestive enzymes and release them into the duodenum. The endocrine units of the organ, the Islets of Langerhans, are embedded in exocrine tissue and contain four distinct cell types. The great majority of islet cells are centrally positioned insulin-producing β cells. In the periphery, glucagon-producing α cells, somatostatin-secreting δ cells and PP cells for synthesizing pancreatic polypeptide are found. These hormones mediate regulation of blood-glucose levels.

The genetic regulation that underlies endocrine pancreas development is still under intensive investigation. The first-known major step initiating pancreatic organogenesis is an induction event. The notochord touches the duodenum, and mesodermal activin repels endodermal *Shh* activity [4–6]. This allows *Pdx1* expression to mark duodenal cells, which later in development give rise to the dorsal pancreatic outgrowth. A second, ventral out-

growth, however, is induced differently, since it is independent of the notochord [7–9]. Upon activation of *Pdx1*, other genes, e.g. *Hlxb9*, *Hnf6*, *Foxa1*, *Foxa2*, *Hnf1α*, *ngn3*, *NeuroD/BETA2*, *Pax6*, *Pax4*, *Nkx2.2*, *Nkx6.1*, *Mist1* and *p48*, influence further cell fate decisions within the developing organ [10–25]. For example, the choice between duodenal and exocrine cell fate is influenced by *p48* [26]; *Hnf6*, *ngn3*, *NeuroD/BETA2* and *Pax6* mediate the switch between an exocrine and endocrine cell fate [27]. Since all of the genes mentioned are transcription factors, they operate by binding to regulatory DNA sequences of target-gene promoters [28–32].

The genetic information of an individual is identical within every single cell of an organism. As a consequence, a distinct pattern of transcription factor expression dictates the fate of a given cell by acting on cis-regulatory DNA sequences. Consequently, it is possible to deduce a cell's determination and differentiation status from its observed gene expression pattern. The chain links between this regulatory environment and the executive genes are cis-regulatory elements of genes, and the investigation of gene interactions leading to distinct cell fates will always include research about the according cis-regulatory elements. This review summarizes the scientific results currently available concerning direct gene interactions during endocrine pancreas development and function, emphasizing apparently conserved promoter structures of endocrine genes.

The dual task of *Pdx1*

During pancreatic organ genesis, the homeodomain transcription factor *Pdx1* represents the most important factor for regulation of pancreas development among the currently known genes [2]. Disruption of the *Pdx1*-gene leads to a loss of exocrine as well as endocrine tissue [8, 9]. Together with *Hlxb9* its expression domain appears in the duodenum early in development [8–11] and marks a population of cells that represent the earliest pancreatic precursors [33, 34]. Once activated, *Pdx1* mediates expression of a huge variety of continuative factors [35, 36]. Some of them subsequently are necessary to demarcate distinct cell lineages [20, 21, 27]. To date, direct regulation of three transcription factors by *Pdx1* protein has been described (fig. 1). Cis-regulatory elements that mediate pancreas-specific expression of *Pax4*, *Nkx6.1* and of *Pdx1* itself are regulated by *Pdx1* protein [37–41].

Considering *Pdx1* as a gene on top of a genetic regulatory cascade governing pancreas development – comparable to *Pax6* in eye morphogenesis – it might be expected to directly activate even more transcription factors that are responsible for further fate decisions later in development. However, no direct regulation even of promising candidates such as *Hlxb9*, *Hnf6* or *ngn3* by *Pdx1* has yet been reported.

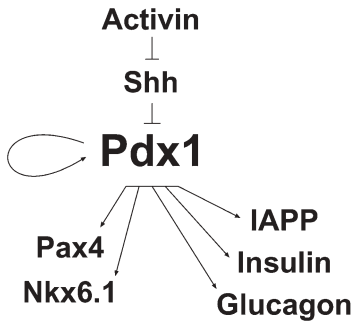

Figure 1. The dual task of *Pdx1*. Early interactions. *Pdx1* has been shown to interact with cis-regulatory elements of transcription factors (*Pdx1*, *Pax4*, *Nkx6.1*) as well as of peptide hormones (IAPP, insulin, glucagon). Activin, repressing endodermal *Shh*, enables *Pdx1* expression in early development. After initiating pancreas development, *Pdx1* participates in regulation of glucose-dependent insulin response in mature β cells.

On the other hand, many data exist regarding *Pdx1*-mediated transcriptional control of peptide hormones in the mature organ (fig. 1). This is the second task of the pancreatic *Pdx1* gene. After initiating pancreas development and being expressed in pancreatic precursors in general, *Pdx1* activity is restricted to β and δ cells [42, 43]. In these cells the protein becomes assigned to tasks concerning cell function throughout adulthood [35, 44–46]. For example, *Pdx1* regulates the cell-specific and glucose-dependent hormone production of insulin [47–49], islet amyloid polypeptide (IAPP) [50, 51] and other factors [52–54].

This dual-task existence makes *Pdx1* an especially interesting candidate gene to investigate the principles of gene regulation. Since *Pdx1* governs early developmental processes as well as function of the mature endocrine pancreas, a regulatory circuit can be proposed. Genes that have been directly or indirectly activated by *Pdx1* will later in development have to tightly control *Pdx1* itself to orchestrate glucose homeostasis. Interestingly, during the islet regeneration process – most probably from duct cells – *Pdx1* is again found at the top of the genetic cascade that triggers this regeneration process [55, 56].

Among the DNA sequences recognized by *Pdx1* protein, one easily recognizes the core sequence TAAT, a typical target for homeodomain-containing proteins. Mutation of these TAAT motifs leads to a loss of *Pdx1* binding [36]. *Pdx1* is able to interact with numerous transcription and cofactors, such as *Hnf1*, E47/*Pan1*, *BETA2/NeuroD*, *Pbx1*, *Meis2*, *Prp1*, *p300* and *Pax6* [39, 46, 57–61] on the protein level. Because of their ability to create complexes with *Pdx1*, these proteins have the potential to influence the DNA-binding and transactivating properties of *Pdx1*. Some of these factors can create a huge variety of different protein complexes with or without *Pdx1*, so that *Pdx1* protein has to compete for contribution to distinct protein complexes [58, 61, 62].

Despite possible variations in the composition of *Pdx1*-containing DNA-binding complexes, the alignment of *Pdx1* targets uncovers striking similarities in their DNA sequences (fig. 2). Obviously acting in a feedback-loop regulation, *Pdx1*-containing complexes have been shown to recognize the following DNA sequences within the *Pdx1* promoter: 5′-GTCCTGCTAATAAACGACTTTTT-3′ (human, nt. –2779 to –2757) and 5′-ACACTT-TAATTGGTTTAC-3′ (human, nt. –2748 to –2727) [37–39].

Regulation of a second transcription factor, *Nkx6.1*, implicates recognition of its promoter by *Pdx1* protein, which binds to the sequence 5′-CCCTCATAAGT-GATAATGATCTAGG-3′ (mouse, nt. –812 to –788) [63]. In contrast to *Pdx1*, which itself remains active in mature β and δ cells throughout adulthood [35], the third known *Pdx1*-regulated transcription factor, paired-box gene *Pax4*, is only transiently expressed during development. *Pax4* is active in early pancreatic precursors and later in maturing β and δ cells. No *Pax4* protein is detectable in mature islet cells [21]. In the *Pax4* gene promoter *Pdx1* recognizes the *Pax4* A2-promoter motif 5′-TTTGAGT-TATGTATAATGTGAG-3′ (human, nt. –1950 to –1926), and this motif is also bound by *Hnf1* protein [40]. In addition, this motif shows a high degree of similarity to DNA sequences within the promoter of the peptide IAPP produced in β and δ cells. In the IAPP promoter the according motif has been named A2/AT2 element [51, 64]: 5′-ACTGATGAGTTAATGTAATAATGACC-3′ (human, nt. –163 to –138). The hormone IAPP is expressed similarly to the late expression pattern of *Pdx1* but in contrast to *Pax4*: the peptide is found in the adult in mature β and δ cells [65–68]. In fact, according to these observations, highly similar motifs recognizing the same factor (*Pdx1*) are present in different genes (*Pax4*, IAPP) that are regulated oppositely within mature islet cells.

Besides the A2/AT2 element another motif within the IAPP promoter, the A1/AT3 motif (5′-GATGGAAAT-TAATGACAGAGG-3′; human, nt. –96 to –76) is bound by *Pdx1* [51, 64]. Another DNA sequence with striking similarity to A2/AT2 can be found within the *Pdx1* promoter (5′-CTGAGTTAATCAAATAAGT-3′; mouse, –818 to –800), but no functional study has been performed yet with this *Pdx1* promoter element. The same is true for further similar motifs appearing in *Nkx6.1*, *ngn3* and *Pax6* promoters [69; C. Brink and P. Gruss, unpublished].

Within the insulin promoter the so-called A3/A4-element [70] is recognized by *Pdx1* in rat [47]: 5′-GT-TAATAATCTAATTAC-3′ (rat, nt. –224 to –207) and mouse [71] 5′-CTTATTAAGACTATAATAACCCTAA-GACTA-3′ (mouse, nt. –220 to –191). These sequences show striking similarity to A2/AT2 as well as the *Pdx1*-binding GLUT2TAAT element [52] of the GLUT2 promoter: 5′-TGACTTAATAATAACAGTA-3′ (human/mouse, nt. –517 to –488). Further interactions have been demonstrated between *Pdx1* and the glucokinase promoter [54, 72] as well as the glucagon-promoter [73], using the promoter sequence 5′-GAACAAAACC-CCATTATT-TACAGATGAGAA-3′ (mouse, nt. –103 to –74). Interestingly, using in vitro assays, it was also possible to show an interaction between *Pdx1* and the non-β-cell promoter of albumin [36]: 5′-TGAAGCTCAGGTTTAATTC-CCAGTCACAT-3′ (mouse, nt. –336 to –308). In vivo, however, the interactions between *Pdx1* and insulin, IAPP, glucagon, *Pdx1* and *Pax4* promoters could be verified, whereas interactions with GLUT2, glucokinase or albumin promoters did not appear [36]. This suggests that chromatin structure has a decisive influence on promoter activity in these cases.

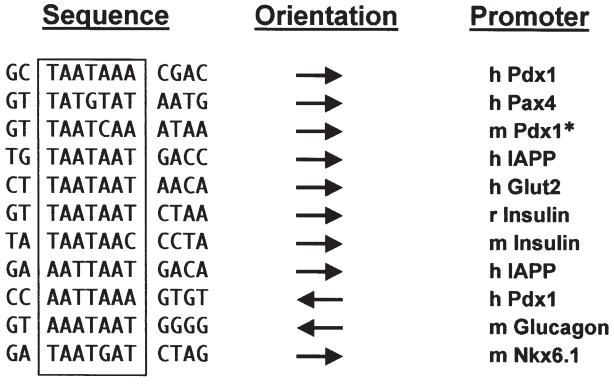

Figure 2. *Pdx1* target sequences. Aligning the DNA sequences that are recognized by *Pdx1* protein reveals a predominance for binding to 5′-TAATAAT-3′ (box). Arrows indicate the orientation of the given sequence within the given promoter. The sequence out of the *Pdx1* promoter that is marked with an asterisk is listed because of its similarity to the other *Pdx1*-targets, but no binding of the protein has yet been shown for this element.

Exocrine or endocrine: *Hnf6, ngn3* and *NeuroD/BETA2*

Early in development the decision between exocrine and endocrine cell fate marks a first bifurcation in the course of pancreas development after induction [74, 75]. There is evidence that onecut-homeodomain transcription factor *Hnf6* [12], the basic helix-loop-helix transcription factors *ngn3* [18] and *NeuroD/BETA2* [19], and also the paired-box transcription factor *Pax6* [20] participate in controlling the switch between endocrine and exocrine tissue [27]. An influence of a *notch-hes1*-mediated mechanism of mutual fate inhibition (fig. 3, red arrows) has been discussed [27, 76].

Except for *Hnf6*, all of these factors are specifically active within endocrine cells. For all of them loss-of-function-analysis was performed, and without exception the phenotypes solely affect endocrine cell types, leaving the

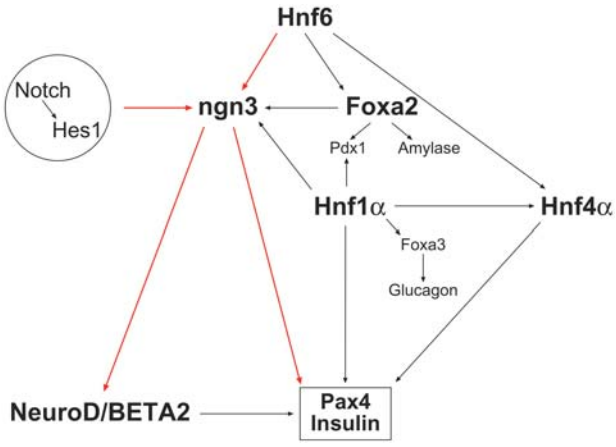

Figure 3. Genetic interactions of pancreatic genes after induction. An overview of the currently known genetic interactions of genes important for development and function of the endocrine pancreas is given. Red arrows mark the genetic network that has been discussed to mediate the decision between exocrine and endocrine cell fate [26]. For *Hnf1α* and *Hnf4α* only the pancreatic regulation pathway is shown; in hepatic tissue the regulation hierarchy between these two factors is inverted [17].

exocrine solely affect normal. On the other hand, *P48* [25, 26] and *Mist1* [24] represent factors which particularly influence exocrine tissue development. Two exocrine cell types can be found: acinar and duct cells [77, 78]. Interestingly, the decision between exocrine and endocrine fate is not necessarily final. At least for regenerative processes, the duct cells seem to represent a link between exocrine and endocrine cell fate [56, 79]. In the following sections, however, this review will focus solely on the endocrine factors. The most important currently known interactions between endocrine genes are summarized in figure 3.

Even though early *Hnf6* activity is visible in epithelial cells that give rise to exocrine as well as to endocrine tissue and later disappears from the islets [80, 81], the loss-of-function phenotype of the gene exclusively shows effects that are restricted to the endocrine part of the organ [12]. Animals missing both functional *Hnf6* alleles lack complete Islets of Langerhans at birth, and at this developmental stage only a few endocrine cells are found. Later, however, perturbed islets may appear, but still the grown-up mice remain diabetic. Interestingly, downregulation of the gene at birth in endocrine cells is also necessary for proper islet formation and function [82]: persistent *Hnf6* expression in islets leads to diabetic mice with disturbed islet architecture and nonfunctional *β* cells.

Hnf6 is regulated by the interplay between growth hormone (GH), *Hnf4α* and C/EBP activity [83, 84]. The mechanism by which *Hnf6* is turned off in mature islets, however, is still unknown.

Currently known downstream targets of *Hnf6* are numerous liver-expressed genes [85] and the pancreatic factors *Foxa2*, *Hnf4* and *ngn3* [12, 79, 86]. Competition between *Foxa2* and *Hnf6* for binding the same target sequences has been discussed [85]. There are two isoforms of *Hnf6*, *α* and *β*, which are both capable of binding as a monomer as well as integrated into complexes [86]. The p300/CREB binding protein-associated factor (p/CAF) is – among others – one possible partner of *Hnf6* in DNA binding [87].

For binding of *Hnf6* the DNA motif 5′-ATNGA-3′ turns out to be most crucial (fig. 4). Out of the *Hnf6*-regulated hepatic genes the consensus binding motif 5′-TTATT GATTT-3′ emerged [85, 86], which is highly consistent with the motifs recognized by *Hnf6* during pancreas development: the *Foxa2* promoter (5′-CGATATTGATTTTT-3′; rat, nt. –139 to –126) and the inverted *Hnf4α* promoter element (5′-AAGTCAATGA-3′, nt. –387 to –378) [84]. It is also similar to inverted *Hnf6*-bound sequences of the *ngn3* promoter (5′-AAATC-CATGT-3′; mouse, nt. –3187 to –3178 and 5′-GCATC-CATAG-3′; mouse, nt. –453 to –444) [12]. A summary of the *Hnf6*-bound DNA motifs is depicted and discussed in figure 4.

Out of all *Hnf6*-regulated genes, *ngn3* seems to represent the most important factor lining up the main switch for enabling islet development – comparable to the role of *Pdx1* at the beginning of pancreas development [88]. Like *Pdx1*, *Ngn3* is capable of inducing endodermal outbudding upon ectopic endodermal expression. Within these buds, *ngn3* mediates the differentiation of endocrine cells that form islet structures, whereas ectopic *Pdx1* induces an – at least partial – pancreatic cytodifferentiation [88]. This observation is evident since it has been shown that *ngn3*-expressing cells are islet progenitors, whereas pancreas progenitors are marked by *Pdx1* expression [89]. Without *ngn3* activity, no endocrine cell types are present [18]. Besides *Hnf6*, the factors *Hnf1α* and *Foxa2* as well as the notch-regulated *Hes1* bind to the *ngn3* promoter and influence its expression rate [90].

As a member of the *bHLH* family of transcription factors *ngn3* directly influences the expression of another islet specific *bHLH* gene, *NeuroD/BETA2* [29]. A loss of function assay of *NeuroD/BETA2* implicates a phenotype similar to, but less severe than, *ngn3*, leading to a diminished number of all endocrine cell types [19].

Sequence	Orientation	Promoter
TTATTGATTT	→	Consensus liver
ATATTGATTT	→	r Foxa2
TCATTGACTT	←	Hnf4α
CTATGGATGC	←	m ngn3 prox
ACATGGATTT	←	m ngn3 dist

Figure 4. *Hnf6* target sequences. The *Hnf6* target sequences and their orientation in the particular promoter are given. The core sequence 5′-ATNGA-3′ emerges from all *Hnf6*-bound motifs.

Both *bHLH* factors, *ngn3* as well as *NeuroD/BETA2*, have been shown to contribute to protein complexes which regulate the β- and δ-cell-specific transcription factor *Pax4* [40] and the insulin gene [91–94] by binding the so-called E1 motif [70], an E-box sequence within the gene promoters [41, 70]. Like the A2 motif, the E1 element is a cis-regulatory element which in the pancreas plays an important role in the transcriptional control of two diverse genes: *Pax4* as a developmental control gene and the peptide hormone insulin. The E1 elements of both promoters are related not only in their structure but also in biochemical function concerning the binding of protein complexes [40, 41]. Besides the *Pax4* promoter, the E1-type E-box motif can be also found and features striking identities in every investigated insulin promoter so far [70]. Interestingly, the sequence found within the *Pax4* gene promoter [41] (5′-AGCAGATGGC-3′; mouse, nt. –1950 to –1941) appears to be inverted in comparison to the motif of the insulin promoter [95, 96] (5′-GCCATCTGCT-3′; rat, nt. –100 to –91). E1 elements of other insulin (insulin I) genes are [70, 97–99]: 5′-GCCATCTGCC-3′ (mouse, nt. –106 to –97), 5′-GCCATCTGCC-3′ (rat, nt. –112 to –103) and 5′-GCCATCTGCC-3′ (human, nt. –111 to –102). The core sequence CATCTG representing the E-box motif (CANNTG) [30, 100] further shows up within the glucagon promoter [96, 101]. E-box motifs in general are present in many other pancreatic promoters [102–105] – among others in *Pdx1* [106] – and are mostly recognized by *NeuroD/BETA2* [30, 107] or by other *bHLH* proteins, for example *ngn3* [29, 40].

Binding of a substantial protein complex could be demonstrated by performing investigations upon the E1 element of the insulin promoter [108, 109]. Within this complex *NeuroD/BETA2* – or *ngn3* – in combination with the *E2A* gene products E47, E12 and E2/5, and *HEB* gene products, bind to the insulin-E1 sequence [110]. Even though these ubiquitously expressed cofactors are not necessary for the interaction between *NeuroD/BETA2* and E1 element [111, 112], this protein machinery-influencing polymerase II activity seems to be conserved among several regulatory processes on the biochemical level [93, 113]. The effect of the *NeuroD/BETA2* complex on polymerase II activity by binding to the E1 sequence has the potential to be positively as well as negatively influenced by factors such as *p300* [93] and c-*jun* or adenovirus E1A [114–116], respectively. These observations point up the regulatory potential of the *NeuroD/BETA2*:*E47* protein complex. Moreover, recently supplied evidence for an interaction between the E1-binding complex and the *Pdx1* protein, which binds the neighboring A3/4 motif, of the insulin promoter throws light on a complex regulation mechanism, at least for insulin expression [61]. A scheme for possibly according interactions between the proteins acting on the neighboring A2 and E1 elements of the *Pax4* promoter is shown in figure 5. The inhibiting activity of adenovirus E1A is mainly based upon the disturbance of the interaction between p300 and *Pdx1* [61].

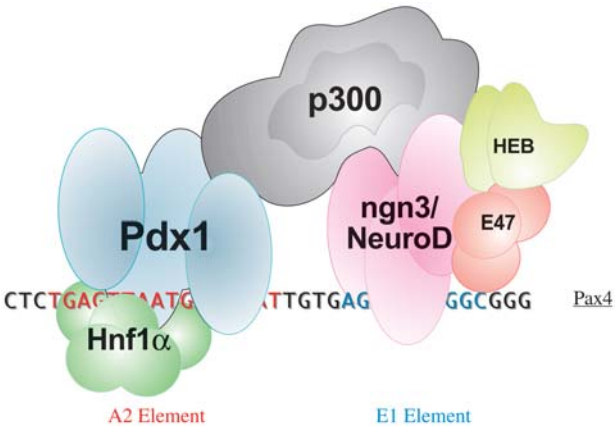

Figure 5. Scheme of protein complexes binding and potentially interacting on the A2 and E1 elements in the *Pax4* promoter. Within the insulin promoter an interaction between the E2-element binding protein complex (*NeuroD*:E47) and A3/4 element-bound *Pdx1* has been demonstrated [58]. Within the *Pax4* promoter *Pdx1* and *Hnf1α* have been shown to recognize the A2 element, and NeuroD was identified as a member of the neighboring E1-element-binding protein complex [37]. The p300 coactivator was shown to mediate an interaction between both complexes. These observations suggest a similar interaction takes place within the *Pax4* promoter.

Taken together, three observations make it tempting to speculate that in this case identical biochemical mechanisms might be the basis of oppositional effects: First, in contrast to *Pax4*, insulin is expressed in mature β cells after birth. Second, both genes contain adjacent E1- and *Pdx1*-binding A2 elements in their promoters. Third, in comparison with the insulin promoter the E1 element of the *Pax4* promoter is inverted [41].

Winged-helix transcription factors

Many genes originally described as hepatocyte nuclear factors (*Hnf* genes) also play a role in endocrine pancreas development and function [117, 118]. Whereas the *Hnf6* gene is characterized by a bifunctional onecut-type homeodomain [12, 28], other members of the *Hnf* gene family, *Hnf3α, Hnf3β* and *Hnf3γ*, belong to the winged-helix class of transcription factors [119–121]. Therefore they have been renamed *Foxa1*, *Foxa2* and *Foxa3*, respectively [122]. *Foxa1* is important for α-cell function [13]. It has been shown to recognize and regulate the glucagon promoter by binding the G2 element (5′-AGGCACAAGAGTAAATAAAAAG-TTTCCGGGCCTCTG-3′; rat, nt. –200 to –164) [123]. *Foxa2*, on the other hand, plays an important role in early endoderm development [124], and its malfunction could be linked to pancreatic disorders [125]. Because of a severe phenotype that leads to early

lethality, insight into the role of *Foxa2* in pancreas development and function emanates from conditional gene-targeting experiments. The factor appears to be necessary for β cell function [126]. *Foxa2* interacts with the *Pdx1* promoter [36, 104, 127–130] at sequences 5′-CCGTTTTTGTTTATTTATCCA-3′ (mouse, nt. –2713 to –2693), 5′-CTTTTTTGTTTATTTATCCATA-3′ (human, nt. –2727 to –2706), 5′-GTGCTAAGCAAACATCCT-3′ (mouse, nt. –2013 to –1996), 5′-AGTGCAAAGTAAACACTCCGG-3′ (human, nt. –2102 to –2122) and 5′-GAACAGAAAGTAAATAAGCGC-3′ (mouse, nt –5927 to –5907); 5′-GGTATTTATTTATATATATATATATAT-3′ (human, nt. –3591 to –3565). In the *ngn3* promoter [90] *Foxa2* binds to 5′-TTATTATTATTTTAGCAAACACTGGAGACAG-3′ (human, nt. –3699 to –3669) and 5′-GATCTCTCGAGAGAGCAAACAGCGCGGCGG-3′ (human, nt. –200 to –170). Also, an interaction with the promoter of the exocrine factor amylase has been described at recognition site 5′-CTGTACCTTAAATATTTACTCATGAGCATTTA-3′ (mouse, nt. –89 to –58) [131]. In general, the consensus recognition sequence 5′-(G/A/C)A(T/A)T(A/G)TT(T/G)(A/G)(T/C)T(T/C)AGTC-3′ emerged, to which *Foxa2* binds as a monomer [132–134]. An alignment of *Foxa2* binding sites is depicted in figure 6.

Foxa1 and *Foxa3* bind to the same or similar sequences. The glucagon G2 element, for example, is a target of both genes [135]. The current results suggest that *Foxa3* does not play a role in the developing pancreas, but after birth a mild phenotype appears upon gene targeting: mature islets of loss of function mice show defective functions which are due to the missing regulation of Glut2 by *Foxa3* in differentiated cells [136].

Sequence			Orientation	Promoter
T	TGACTTAGT	C		crist.
AAT	TGTTTATTT			cons.
TTT	TGTTTATTT	ATCC	→	m Pdx1
GAG	TGTTTACTT	TGCA	←	h Pdx1
GGA	TGTTTGCTT	AGCA	←	m Pdx1
CGC	TGTTTGCTC	TCTC	←	h ngn3
CAG	TGTTTGCTA	AAAT	←	h ngn3
GCT	TATTTACTT	TCTG	←	m Pdx1
AAA	TATTTACTC	ATGA	→	m amylase
TTT	TATTTACTC	TTGT	←	r glucagon G2
GGG	TATTTATTT	ATAT	→	h Pdx1
AAA	TATTTAAGG	TACA	←	m amylase

Figure 6. *Foxa2* target sequences. An alignment of the *Foxa2*-recognized DNA sequences within pancreatic promoters shows similarities with the consensus of the *Foxa2*-bound motifs of hepatic genes (cons.). Surprisingly, crystallographic analysis has led to identification of a highly divergent DNA sequence serving as *Foxa2* target (crist.). Sequences and orientation within the promoters are given, respectively. Highest conservation can be found for the core sequence 5′-TGTTTNNT-3′.

Hnf1 and *Hnf4*

The transcription factors *Hnf1*α, *Hnf1*β and *Hnf4*α play essential roles in pancreas development and function [137–140]. *Hnf1*α, like the related gene *Hnf1*β, contains a homeodomain-like DANN binding domain [141–143]. No functional role for *Hnf1*β in pancreas development has yet been reported [144–146], but malfunction of the gene was linked to pancreatic disorders [147–152]. Further, a pancreatic tissue-specific effect on the P2 promoter of the *Hnf4*α gene could be demonstrated [153]. *Hnf1*β recognizes the same target sites as *Hnf1*α, and they bind DNA as homo- or heterodimers [154, 155], for example during recognition of the P2 element of the *Hnf4*α gene and during regulation of the insulin A3 element [156].

Especially interesting is the regulation of the P2 promoter element 5′-AGTGACTGGTTACTCTTTAACGTATCCAC-3′ (human, nt. –93 to –65) [17], since it drives the expression of an islet-specific splice variant of *Hnf4*α in differentiated islet cells [17, 153]. This process inverts the regulation pathway that has been described during liver development, where *Hnf1*α lies downstream of *Hnf4*α [157–159].

An important role for *Hnf1*α itself during pancreas development directly emerged from several loss-of-function studies [160–169]. Accordingly, the interactions between *Hnf1*α and several promoters mediating pancreatic gene activity have been described, and effects on the transcriptional control of *Foxa3* (5′-TGTTAATAGTTAACC-3′; mouse, +16 kb) [170], *Hnf4*α and the factors glut2 and pklr by *Hnf1*α were shown [17]. Further *Hnf1*α target sequences exist within the *Pdx1* gene, where the previously described *Foxa2* target [130] and the sequence 5′-GTCCTGCTAATAAACGACTTTTT-3′ (human, nt. –2763 to –2741) [37] are recognized. As mentioned, together with *Hnf1*β the A3 element of the insulin promoter at 5′-TGGTTAAGACTCTAATGACC-3′ (human, nt. –231 to –211) [156, 171] can be bound by *Hnf1*α. In the *ngn3* promoter the target sequence 5′-CTTGTAATTATTTATTAAACGAAATCT-3′ (human, nt. –3728 to –3702) [90] and in the *Pax4* promoter the target 5′-TTGAGTTAATGTATAATTGTGAGCA-3′ (human, nt. –1950 to –1926) [40] are recognized. The favored liver-specific *Hnf1*α recognition sequence consensus is GGTTAATNATTANCA [172, 173], which shows high identity to the pancreas-specific sites. In general, there seem to exist two recognition sequences that can be used by *Hnf1*α as DNA targets. The first represents the partial palindrome 5′-GGTTANNNTTANC-3′; the second deviates from this consensus to preferentially recognize 5′-TTAATAAATA-3′. Alignment of the *Hnf1*α recognition sequences is shown and discussed in figure 7. Still, *Hnf1*α has the potential to contribute to the regulation of many more pancreatic genes [174]. This potential may include the in-

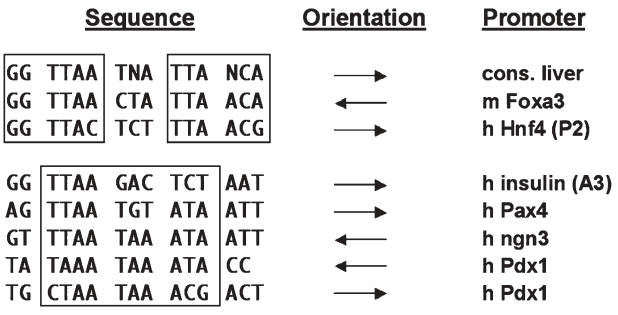

Figure 7. *Hnf1α* target sequences. The currently described *Hnf1α* target DNA sequences are aligned, and the corresponding orientation in the according promoter is given. Two motifs emerge from this alignment: First, the incomplete palindrome 5′-GGTTAANNNT-TANC-3′ emerges. Second, a consensus sequence similar to the motif 5′-TTAATAAATA-3′ can be recognized within another group of *Hnf1α* targets. Tissue-specific regulation of the P2 promoter element within the *Hnf4* promoter shows that these two target motifs are not representing tissue-specific promoter elements, since the pancreas-specific P2 promoter uses the palindrome target sequence, which is highly similar to the consensus sequence recognized by *Hnf1α* protein in liver tissue (cons. liver).

volvement of further cofactors like it has been shown for p300 on the Glut2 promoter (nt. +200 to +218) [175].

The *Hnf4*-genes are members of the nuclear hormone receptor superfamily and contain a zinc-finger DNA binding motif [176]. Several isoforms of *Hnf4* represent related genes (*Hnf4α, β, γ*), but splice variants have also been described [177, 178]. *Hnf4β* and *Hnf4γ* turned out to recognize *Hnf4α*-binding DNA motifs and have been shown to exhibit an expression pattern similar to the previously detected *Hnf4α* [118, 140, 179, 180]. *Hnf4α*-to-DNA binding occurs exclusively as homodimers [181, 182], is phosphorylation dependent [183] and can be influenced by coactivators [184]. *Hnf4α* is involved in numerous developmental and regulatory processes: loss-of-function studies revealed its important role in its expression domain, the visceral ectoderm, in early development [185–187]. *Hnf4α* is further present in mature pancreatic islets [188] and is necessary for islet function [189–191]. From the sites recognized by *Hnf4α* in hepatic genes, the preferred consensus 5′-GGGCCAAAGGTCA-3′ emerged

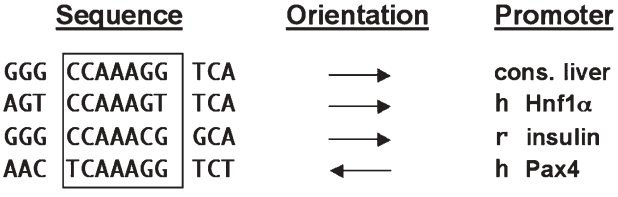

Figure 8. *Hnf4α* target sequences. Alignment of *Hnf4α* target DNA sequences shows the similarity between motifs within hepatic and pancreatic genes (box). The sequence and orientation within the given promoter are indicated. The core sequence 5′-CAAA-3′ is consistent within all *Hnf4α*-bound motifs.

[192], which is mirrored, for example in the binding site of the *Hnf1α* promoter: 5′-AGTCCAAAGTTCA-3′ (human, nt. –66 to –48) [193]. *Hnf4α* influences the expression rate of several pancreatic genes [194]. A direct interaction between *Hnf4α* and cis-regulatory elements of pancreatic promoters could be shown for the *Pax4* promoter (5′-GTGGCAAGACCTTTGAGTTAA-3′; human, nt. –1960 to –1940) [40] and for the insulin promoter (5′-GCCCTTAATGGGCCAAACGGCAAAGTCCAGG-3′; rat, nt. –84 to –54) [195]. The *Hnf4α* target DNA sequences are assembled and discussed in figure 8.

Pax transcription factors

Two members of the *Pax* family of transcription factors, *Pax4* and *Pax6*, have been shown to be crucial for cell identity and islet architecture within the endocrine pancreas [196–198] and for gastrointestinal endocrine cell development [199]. Without *Pax4* no *β* cells, in a *Pax6* loss-of-function animal no *α* cells and no islet structures form within the organ, and the total number of endocrine cells is reduced [20, 21, 200]. Several splice variants of *Pax4* have been described that might achieve oppositional effects, respectively [201, 202]. However, *Pax4* was shown to act as a transcriptional repressor gene [203–206], possibly binding to and competing for the same motifs as *Pax6* [207]. By affinity selection to random oligonucleotides the bipartite recognition sequence 5′-AAAATTA-N15-(C/T)CACCCC-3′ emerged, and similar motifs in hormone gene regulatory elements are bound by *Pax4* protein [203]. *Pax4* has been shown to bind the sequences 5′-GCCAGACCTGTCCCTGCTCACAGCT-3′ (human, nt. –262 to –238) in the insulin and to possibly act on 5′-ACTTTCTATCTATAGGGATG-3′ (human, nt. –111 to –92) in the IAPP promoter [205, 64]. In another study the binding motif 5′-GCANTCANGCGTGAA-3′ for the *Pax4* and other paired domains and the palindrome 5′-TAAT-N_{1-5}-ATTA-3′ for the *Pax4* and other homeodomains have been described [208]. For *Pax6* several binding sequences emerged that show similarities to the *Pax4* binding sites. Three different studies describe *Pax6*-binding sequences, that have been selected by their affinity for *Pax6* protein: T5′-ANNTTCACGC(A/T)T(G/C) ANT(G/T)(A/C)NT-3′ [209], 5′-(G/A)NG(C/A)ANT (G/C)A(A/T)GCGT(G/A)AA-3′ [210] and 5′-TTAGT-TCCAG GTCAG-3′ (present in a human soluble guanylate cyclase large subunit intron) [211]. *Pax6* was further shown to directly bind the *Pdx1* promoter (5′-AATAAAT-GAAGCGTCGAGAT-3′; mouse, nt. –2071 to –2052) [127]. On the G1 element (5′-CCCCATTATTTACAGAT-GAGAAATTTATATTGTCAGCGTAATATCTGCAAG-GCTAAACAG-3′; rat, nt. –94 to –34) of the glucagon promoter *Pax6* builds a complex with *Cdx2*-, *MafA*- and *p300*- protein [211–215]. The glucagon

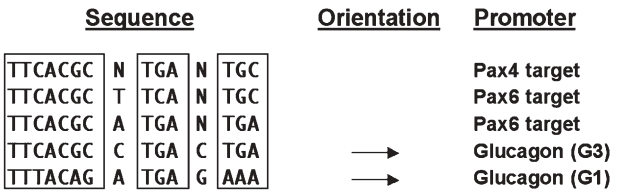

Figure 9. Target DNA sequences of *Pax4* and *Pax6*. Target sequences for *Pax4* and *Pax6* have been described based on their ability to bind protein as random PCR (polymerase chain reaction) fragments. Additionally, the glucagon promoter sequences G1 and G3 have been described as *Pax6* targets and fit to the consensus sequences of these findings. However, in the alignment depicted, only the most similar outcome of investigations upon *Pax*-targets is shown. Further potential targets can be found, some of them showing a bipartite consensus. Details about these motifs can be found in the text.

G3 element (5′-TTTTTCACGCCTGACTGAGATTGAAGGGTGTA-3′; rat, nt. –265 to –240) contains a sequence motif that is responsible for islet-cell-specific expression of insulin, glucagon and IAPP (5′-CGCCTGA-3′), and is also recognized by *Pax6* [216–218]. The similarity of the particular sequences is given as an alignment in figure 9.

A third *Pax* gene, *Pax2*, might also contribute to pancreas development. However, no functional analysis of *Pax2* in the pancreas has been performed yet, but it has been shown to be expressed in pancreatic islets and to transactivate glucagon. It binds the glucagon G1 element with lower and the G3 element with higher affinity than *Pax6* [219]. A screen for *Pax2* targets additionally revealed the recognition motifs 5′-GNNTTAANTCAAGTGANACAGTT-3′ [220], 5′-TCA(T/C)GC(A/G)TGACNA-3′ [221] and for the paired domain 5′-(G/C)AAAC(T/A)C-3′ [222].

Nk transcription factors

Nkx2.2 and *Nkx6.1* have been demonstrated to have decisive influence on maturation of pancreatic islet cells [22, 23, 223]. They both belong to the NK type of homeobox genes [224]. *Nkx2.2* directly regulates *Nkx6.1* [23, 225]. In the *Nkx6.1* promoter *Nkx2.2* recognizes the sequences 5′-CCCTCATAAGTGATAATGATCTAGG-3′ (mouse, nt. –812 to –788) in parallel to *Pdx1* and is also able to recognize 5′-CGGAAGAGACGCACTTAAACTGCTTTTC-3′ (mouse, nt. –478 to –441) [63]. *Nkx6.1* acts as a repressor on the insulin promoter and recognizes the sequence 5′-TTAATTAC-3′, (5′-AATCTAATTACCCT-3′; rat insulin A3/A4-element), but the COOH terminus inhibits this interaction [63, 226].

Hlxb9, *Isl1*, *Cdx2* and *MafA*

The homeobox gene *Hlxb9* has been shown to play an important role in pancreas development and function, mainly according to the dorsal part of the organ [227–230]. Despite this fact no search for *Hlxb9* target sequences has yet been performed.

Developmental function of the LIM-domain homeobox transcription factor *Isl1* affects the pancreas and the surrounding mesenchyme [231], and it also plays a role for islet function [232]. It has been shown to bind the insulin promoter at 5′-TTAATAATCTAATTA-3′ (rat, nt. –222 to –208) [233]. The somatostatin promoter is recognized at 5′-TTGCGAGGCTAATGGTG-3′ (rat, nt. –104 to –88) [234, 235]. *Isl1* binds the IAPP promoter at 5′-GAGTTAATGTAATAATGACC-3′ (human, nt. –156 to –137) [236] and the glucagon promoter at several sites within the G1 element (see above) [237].

Cdx2, one of three caudal homologues in vertebrates, plays an important role in early development and is regulated by *Oct1* [238–242]. In endocrine cells it has been shown to autoregulate itself by using the sequences 5′-GTAAACACTCGTTAATCACGTAAGGC-3′ (mouse, nt. –18 to +18) and 5′-TGTGTCATTACTAATAGAGTCTTGTA-3′ (mouse, nt. –41 to –16) [243]. *Cdx2* activates glucagon expression by interaction with *Pax6* and p300 on the G1 element (see above), where the motifs 5′-TAAATATAA-3′ and 5′-ATTATA-3′ are crucial [244–248]. Further recognition of *Cdx2* has been demonstrated for the insulin promoter (5′-TGTTAATAATCTAATTA-3′; rat, see above) [249], as for many more AT-rich elements in various promoters, such as 5′-AATAAAACTTTAT-3′ [241], 5′-TATTTTA-3′ [250], 5′-TATTTTACAA-3′ [251], 5′-TAAAGACTATAAAA-3′ [252, 253], 5′-TTTTAT-3′, 5′-TAATTGTTTTATGGTTTAA-3′ [254] and more [255–258], with one example including an interaction with *Hnf1α* [259].

The basic leucine zipper gene *MafA*, known as a phosporylation-dependent downstream target of *Pax6* in lens development, has recently been shown to bind the insulin promoter RIPE3b1 element at 5′-TGGAAACTGCAGCTTCAGCCCCTCTG-3′ (human, nt. –126 to –101) [260–262].

Conclusion

The development of the endocrine pancreas is an important and growing field of research. Learning about the genetic program that underlies the differentiation, regeneration and function of distinct endocrine cell types will enhance our potential to cure hormonal diseases arising from pancreatic disorders.

This review summarizes the currently known cis-regulatory DNA sequences and the transcription factors and pro-

tein complexes that play a role in endocrine cell differentiation and function. Apparently, in numerous cases the motifs recognized by a certain protein or protein complex in different promoters feature striking similarities. Such sequences might serve as templates for screening further pancreatic promoters, helping to achieve initial hints about possible regulatory elements. Large motifs that are highly consistent might even be used for screening large genomic sequences or even genomes for pancreatic factors: since several genomes have been sequenced, 'reverse genetics' have become a potent tool of life science. A combinatory screen 'in silico' for open reading frames and certain neighboring cis-regulatory elements will be a future way of identifying new genes and their field of activity before even knowing their biochemical identity. But the biochemical mechanisms of many transcription factors and protein complexes influencing transcription still need to be elucidated and will lead to the detection of even more genes influencing pancreas development.

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