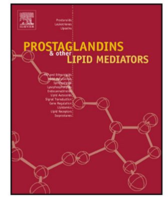
Prostaglandins & other Lipid Mediators 121 (2015) 70–82

Contents lists available at ScienceDirect

Prostaglandins and Other Lipid Mediators



Original Research Article

Prostacyclin receptors: Transcriptional regulation and novel signalling mechanisms

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ARTICLE INFO

Article history:
Received 30 January 2015
Received in revised form 25 March 2015
Accepted 18 April 2015
Available online 30 April 2015

Keywords:
Prostacyclin receptor
Estrogen receptor
Sterol response element binding protein (SREBP)
PDZK1(PDZ-domain-containing protein 1)
IKEPP (intestinal and kidney enriched PDZ protein)
C/EBP, CCAAT/enhancer binding protein
Rab11
Gene
Cardiovascular

ABSTRACT

The prostanoid Prostacyclin plays diverse physiologic roles within the vasculature and other systems, and is widely implicated in several cardiovascular, pulmonary and renal diseases. Despite this, knowledge of the factors regulating expression of the I prostanoid receptor (the IP) remained largely unknown. This review details recent advances in understanding the key transcriptional regulators determining expression of the PTGIR gene in the human vasculature and the identification of novel interacting partners of the IP that impact on its function therein. Included in this are the *trans*-acting factors that regulate expression of the PTGIR under basal- and regulated-conditions, particularly those determining its up-regulation in response to cellular differentiation, estrogen and low serum-cholesterol. Moreover, the functional implications of the interactions between the IP with PDZK1, a multi PDZ-domain containing protein essential for reverse-cholesterol transport and endothelialization, and the IP with IKEPP, the intestinal and kidney enriched PDZ protein, for the role of the prostacyclin-IP axis within the vasculature are reviewed.

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1. Introduction

The prostanoid prostacyclin, also referred to as prostaglandin (PG)I_2, plays an essential role in haemostasis and in the dynamic regulation of vascular tone acting as a potent inhibitor of platelet aggregation and as a dilator of vascular smooth muscle [1–4]. It also exerts potent *pro*-inflammatory and *anti*-proliferative effects [5–7] and promotes vascular repair following endothelial injury [8]. Hence, prostacyclin plays a key protective role in the vasculature and imbalances in the levels of prostacyclin, or of its specific synthase or its receptor, are implicated in a diverse range of cardiovascular diseases (CVDs) including thrombosis, stroke, myocardial infarction, atherosclerosis, systemic and pulmonary hypertension [3,6,7]. In addition to its role in the vasculature, prostacyclin is centrally involved in other systems including in the kidney where it regulates renal blood flow and glomerular filtration rates [9,10], and in the lung where it acts as a bronchodilator and is widely indicated in the treatment of pulmonary arterial hypertension [11,12].

Consistent with its role in the vasculature, prostacyclin is mainly produced within the endothelium and vascular smooth muscle where it is synthesised from arachidonic acid predominantly by the sequential actions of cyclooxygenase (COX)1 or COX2, to generate the intermediates PGG_2/PHG_2 and subsequently by prostacyclin synthase to yield prostacyclin [2,13–18]. The actions of prostacyclin are mainly mediated through its specific cell surface prostacyclin receptor or, more properly according the IUPHAR nomenclature, the I prostanoid receptor or, in short, the IP, a

Abbreviations: AoSMC, human aortic smooth muscle cell; CAD, coronary artery disease; C/EBP, CCAAT/enhancer binding protein; ChIP, chromatin immunoprecipitation; COX, cyclooxygenase; CVD, cardiovascular disease; EC, endothelial cell; ER, estrogen receptor; ERE, estrogen response element; GIP, GPCR interacting protein; GPCR, G protein-coupled receptor; HEL, human erythroleukemia; HUVEC, human umbilical vein endothelial cell; IKEPP, intestinal and kidney enriched PDZ protein; IP, prostacyclin receptor; NHERF, NA^+/H^+ exchange regulatory factor; PDZ, Postsynaptic density-95, Discs large, Zonula occludens-1; PDZD, PDZ domain; PDZK1, PDZ-domain-containing protein 1; PKA, cAMP-dependent protein kinase A; PMA, phorbol 12-myristate 13-acetate; pGL3B, pGL3Basic; pRL-TK, pRL-thymidine kinase; PRR, PMA-responsive region; PTGIR, prostacyclin receptor gene; PTGS2, COX2 gene; RBD, Rab11 binding domain; RCT, reverse-cholesterol transport; RLU, relative luciferase unit; SEM, standard error of the mean; SNP, single-nucleotide polymorphism; SRE, sterol response element; SREBP, sterol response element binding protein; TAF, TATA-box binding protein associated factor; TBP, TATA-box binding protein; $TF_{II}D$, transcription factor D for RNA polymerase II; TI, transcription initiation; SDM, site-directed mutagenesis; TX, thromboxane; URR, upstream repressor region; Y2H, yeast-two-hybrid.

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http://dx.doi.org/10.1016/j.prostaglandins.2015.04.008
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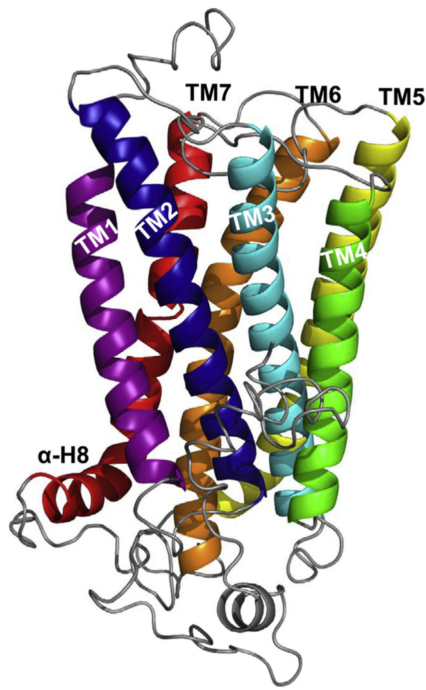

Fig. 1. Structure of the Human Prostacylin Receptor.
Three-dimensional representation of the human IP, depicting the seven transmembrane (TM) domains, TM1 to TM7, and the alpha-helical 8 domain (α-H8). The structural prediction was generated by online submission to the iterative TASSER (I-TASSER) algorithm, that builds three-dimensional protein structure models based on multiple threading consensus target-to-template alignments by LOMETS.

member of the G protein coupled receptor (GPCR) superfamily [4]; Fig. 1). The IP is predominantly coupled to Gs-activation of adenylyl cyclase, increasing cellular cAMP and, in turn, activation of cAMP-dependent protein kinase (PK) A to mediate many of the inhibitory actions of prostacyclin in platelets and in various types of smooth muscle (SM), including vascular (V) SM [2]. In addition to the IP, prostacyclin can act as a weak agonist of PPARδ, a member of the peroxisome proliferator-activated receptor (PPAR) family of nuclear receptors, particularly at elevated concentrations [19–23].

The importance of prostacyclin in protecting against CVD was highlighted by the finding that certain COX2-selective inhibitors/COXIBs, such as Vioxx, were associated with increased clinical incidence of thrombosis, myocardial infarction and/or stroke due to their selective impairment of prostacyclin synthesis without affecting levels of the *pro*-thrombotic thromboxane $(TX)A_2$, a prostanoid predominantly synthesised by COX1 in the anucleated platelet [24]. Hence, though remaining somewhat controversial, the "imbalance theory" proposes that COXIBs may shift the balance between the *anti*-thrombotic prostacyclin and the *pro*-thrombotic TXA_2, thereby increasing the incidence of adverse thombotic episodes in certain individuals [13,14,16–18]. In line with this, $IP^{-/-}$ null mice display enhanced tendency toward thrombosis, intima hyperplasia, atherosclerosis, and restenosis [25,26]. Furthermore, endothelial progenitor cells (EPCs) from $IP^{-/-}$ null mice fail to promote re-endothelialization and vessel repair in an experimental model of endothelial injury [8]. Hence, the prostacyclin-IP axis plays a central protective role in promoting re-endothelialization, limiting neointima hyperplasia and vascular remodeling in response to the vessel wall injury that frequently accompanies atherosclerosis or certain vascular/surgical procedures, such as angioplasty or carotid endarterectomy for example [8]. Somewhat consistent with this, several single-nucleotide polymorphisms have been identified within the IP gene that predispose individuals to CVD, including enhanced risk of deep vein thrombosis and intimal hyperplasia [27]. However, despite this extensive appreciation of the importance of prostacyclin and its receptor, the IP, for vascular integrity, detailed knowledge of the factors regulating expression of the IP gene, the PTGIR, within the vasculature or indeed within any other system in which the prostacyclin-IP axis is physiologically important, remained poorly understood. This review details some of the recent advances that have led to the current understanding of the key transcriptional regulators determining expression of the human PTGIR within the vasculature, where studies were largely carried out in vascular model systems including in the megakaryoblastic platelet-progenitor human erythroleukemic (HEL) 92.1.7 and in the endothelial EA.hy 926 cell lines, in primary (1°) human umbilical vein endothelial cells (HUVECs) and/or in 1º human aortic smooth muscle cells (hAoSMCs).

2. Transcriptional regulation of IP expression

2.1. Identification of the core promoter region of the human PTGIR

The structural organization of the human IP gene, the PTGIR, located on chromosome 19q13.3 is depicted in Fig. 2A. In brief, it is composed of 3 exons separated by 2 introns [28], where exon (E) 2 and E3 are the main coding exons. E1, on the other hand, exclusively encodes 5′ untranslated region (UTR) where, within E1, the major transcriptional initiation (TI) site maps approximately to nucleotide -917 upstream of the translational initiation codon [28,29]. The human IP promoter, here-on-in referred to as the PrmIP, lacks a conventional TATA box and initiator (Inr) element [29].

In order to characterize the human PrmIP, a 1.677 kb gene fragment surrounding the TI site was evaluated for promoter activity through a series of luciferase-based gene reporter assays initially in the platelet-progenitor HEL 92.1.7 cell line (Fig. 2A & B) [29]. Using this gene-reporter approach combined with 5′deletional analysis, a series of successive 5′ sub-deletions denoted PrmIP1–PrmIP7 were generated to map the main transcriptionally active regions within the human PrmIP (Fig. 2B). Through this, an upstream repressor region (URR) was identified between PrmIP4 and PrmIP5. Furthermore, it was established that the region between PrmIP6 and PrmIP7 was the smallest sub-fragment with promoter activity and this region was found to correspond to the "*core promoter*" necessary for basal expression of the IP in HEL cells [29]. Likewise in both the vascular endothelial (EA.hy 926 cell line & 1° HUVECs) and aortic smooth muscle (1° hAoSMCs) cell types, the core promoter mapped to PrmIP6 [29,30]. In addition, a URR was identified in the endothelial cell systems but was localised to the region between PrmIP1 and PrmIP2, different to the URR identified in HEL cells and 1° hAoSMCs, located between PrmIP4-PrmIP5. As elaborated upon below, while the *trans*-acting factors that bind and regulate the URR in HEL cells have been recently identified [31], the factor(s) that regulate the endothelial-specific URR remains to be investigated.

In all cell types examined, Sp1, PU.1 and Oct-1 were identified as the key *trans*-acting factors that regulate PTGIR expression through binding to their cognate *cis*-acting elements within the "core promoter/PrmIP6" (Fig. 2C) [29]. As stated, the PrmIP lacks a conventional TATA box and initiator (Inr) element [29]. The ubiquitously expressed transcription factor Sp1 can serve to attract key protein components of the basal transcriptional machinery to promoters lacking a conventional TATA box [32]. The identification of direct interactions between Sp1, TATA-box binding protein (TBP) and TBP-associated factors (TAFs) led to the suggested role of Sp1 as an anchor for TAFs in TATA-less promoters whereby one or more Sp1 molecules bind to G/C-rich regions in such promoters to help establish a transcription pre-initiation complex [33–35]. The PU.1 member of the Ets family [36] is a product of the Spi-1

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