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Review of recent summaries of signalling mechanisms which control gene transcription and translation of the PAS family of plasmin protease stimulators and inhibitors

Przegląd piśmiennictwa dotyczącego mechanizmów sygnałowych kontroli transkrypcji i translacji genów systemu aktywacji plazminogenu

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ABSTRACT

The plasminogen activating system (PAS) plays a key role, in regulating extracellular matrix, during growth, maintenance and repair of all tissues. Consisting of plasminogen activators and inhibitors, it can finely modulate the rate of protein turnover. Extracellular stimuli such as inflammatory and hypoxic mediators, growth factors, and integrins are known to closely interact with cellular signaling pathways in differentially regulating PAS elements. We focus this review to provide an overview of the genetic mechanisms involved in regulating individual elements of this system, as a blueprint for future analysis of involvement of each PAS element in pathological or physiological conditions.

Keywords: Plasminogen activating system, translation, transcription, PAI-1, uPA, uPAR, urokinase, serpine.

STRESZCZENIE

System aktywacji plazminogenu (ang. plasminogen activating system – PAS) odgrywa kluczową rolę w regulacji obrotu macierzy zewnątrzkomórkowej podczas wzrostu, utrzymania i naprawy wszystkich tkanek. Składający się z aktywatorów i inhibitorów plazminogenu, może precyzyjnie modulować tempo obrotu białkami. Wiadomo, że bodźce zewnątrzkomórkowe, takie jak mediatory stanu zapalnego i hipoksji, czynniki wzrostu, i integryny, wpływają na komórkowe szlaki sygnałowe przy regulacji elementów PAS. Skupiamy się w tym przeglądzie na mechanizmach genetycznych zaangażowanych w regulację tego systemu w nadziei zidentyfikowania wyznaczników identyfikacyjnych dla poszczególnych elementów PAS, aby ułatwić bardziej precyzyjną analizę wpływu członków PAS w stanach patologicznych lub fizjologicznych.

Słowa kluczowe: układ plazminogenu, Translacja, Transkrypcja, PAI-1, uPA, uPAR, urokinaza, serpina.

Introduction

The plasminogen-activating system (PAS) has two activators, namely the urokinase plasminogen activator (uPA) and the tissue-type plasminogen activator (tPA), which correspondingly are regulated by specific inhibitors, the plasminogen activator inhibitor 1 (PAI-1) and 2 (PAI-2) which compete for activation of the cell membrane anchored urokinase plasminogen activator receptor (uPAR) (1).

Pathological and physiological processes modulate the rate of secretion of these components through cell membrane detachment (2), clathrin mediated recycling (3), RNA mediated translation interference (4) and transcription attenuation or stimulation (5).

Multiple cancer studies report variable expression of both PAS activators and inhibitors as protective and oncogenic factors (6) owing to a lack of clarity within the metastatic phenotype between stimulation of secretion and stimulation of translation of PAS elements. UPA and PAI-1, since opposite in function, are within a homeostatic feedback with each other (7). Physiological or pathological depletion of one can lead to its upregulation to match normal levels, and a subsequent compensating over expression of the other (8). Experimentally however any depleting mechanism not identified and accounted for in the theoretical framework can result in the levels of the affected and tested for molecule appearing normal, while the

buffering/compensating molecule appearing over expressed if it is even tested for (9). This problem can persist even if the theoretical function of the buffering molecule in the overexpressed state would be biomechanically contradictory to the observed phenotype (10). We observe these problems in studies of fibrosis with regards to uPA (11) and rheumatoid processes with regards to tPA (12), as well as wound healing and plasminogen (13). Quantitative genetic expression studies could resulting in a more certain assessment of upregulation of expression of the target protein. Convergence of signaling pathways between PAS elements makes this process more difficult. Having a wide array of possible interactions as a reference map could help to identify which pathways play a role to achieve a specific effective phenotype which correlates with the studied pathology.

A brief search of the literature shows a variety of environments which stimulate or inhibit the transcription of different combinations of PAS related genes. uPA, uPAR, and PAI-1 gene expression is significantly increased in Adipose Derived Stem Cells (ADSC) from aged patients with Coronary Artery Disease. ADSCs are found to produce more uPAR the older they get. PAI-1 levels in ADSC were found to be proportional to their angiogenic activity (14).

Hypoxia induces PAI-1expression primarily through stabilization and activation of hypoxia inducible factor (HIF-1a), which can transactivate the PAI-1 gene via direct interaction with several hypoxia-response cis-elements in its promoter region (15). Chemically induced stabilization of HIF-1a in normoxia condition is sufficient to mimic the effect of ambient hypoxia on induction of PAI-1 expression in adipocytes (16). HIF drives urokinase-type plasminogen activator receptor (u-PAR) gene expression (encoded by the gene PLAUR) (17,18) however these two studies did not address the issue of identifying a specific pathway for this activation and so the previous summary still stands that the up regulation of PAI-1 via HIF drives an increased production of uPA and uPAR to stabilise the situation. the addition from this article is that loss of uPAR can cause dormancy in human epidermoid carcinoma cells (19).

Contents of cigarette smoke, aromatic hydrocarbons such as Benzo[a]pyrene, were shown to induce expression of plasminogen activator inhibitor-1 in A549 cells, resulting in epithelial to mesenchymal transition (20).

tPA has been reported to stimulate PAI-1 secretion in human lung fibroblasts (21). PAI-1 is one of the furthest downstream target genes of TGFβ/Smad signalling (22). Previous studies have demonstrated that over-expression of PAI-1 can induce fibrosis in many organs, especially in liver, where it can lead to hepatocellular carcinoma (23) and vice versa (24,25) There is also a synergism between EGF and TGFβ to stimulate PAI-1 transcription and translation resulting in a much smaller, concomitant, increase in uPA and uPAR (26). TGF-β isoforms induce intracellular signalling via SMAD-2/3 transcription factors. SMAD-2/3 regulates profibrotic genes, collagens, PAI-1, integrins, TGF and MMPs (27–36). BMP's on the other hand via SMAD-1/5/8 are capable of suppressing fibrotic gene expression of TGF-β's (37).

Bmpr2 knockout causes inhibition of lipopolysaccharide-regulated genes including NFκB and STAT3. It downregulates uPA by 8.1-fold. These factors play a key role in angiogenic and inflammatory remodelling responses, but are also activated during tumour invasion (38).

Lipopolysaccharides cause a significant increase in mRNA expression of uPA, but a decrease in PAI-1, while thrombin and fibrinogen results in an increased expression (39). uPA-gene therapy can activate latent MMPs and single chain-HGF, promoting ECM degradation and hepatic regeneration, and reducing fibrotic tissue in liver cirrhosis (40,41).

Interleukin 1 beta (IL-1b) in peripheral blood-macrophage-conditioned medium (PB-MCM) is the major mediator of uPA expression in chondrocytes. Stimulation of human chondrocytes with peripheral blood-macrophage-conditioned medium was found to induce uPA expression via the JNK/Akt/NF-κB pathway. However, subjected to a lower level of shear stress, PB-MCM-treated chondrocytes showed inhibition of JNK and Akt phosphorylation, NF-κB activation, and uPA expression (42). The shear induced PB-MCM uPA expression was completely stopped with an AMPK agonist.

Lysophosphatidic acid (LPA) is a phospholipid derivative, inducing proliferation, migration and cytokine release via G-protein-coupled-receptors (GPCRs) (43). The common pathway for the LPA up regulation of uPA is via PKC/CARMA3/BCL10/MALT1/NF-κB (24,44–50) of which NF-κB has already been described in (38,51,52)

With the multitude of suggestions from various laboratory groups investigating the influen-

ce of PAS on their own specific application, there are also many suggestions as to their possible biomechanisms. Even within the last decade there are conflicting reports arising from the same fields.

It is therefore worthwhile to see if, since these studies have been published, a reliable reference has collated these reports to highlight any gaps in the literature and provide deeper insights in to the commonalities of the issues present in these case studies.

Aims

Multiple signaling pathways converge on the expression of PAS. Activators and receptors, and in special circumstances activators and inhibitors can be expressed by the same stimulus. The brief literature overview has identified multiple discrete pathways for all the possible modes of PAS activation to resolve the uncertainties presented by conflicting results in single protein studies. Our meta-analysis could show if currently known pathways of activation of PAS related genes have been cross referenced sufficiently in order to create a comparison chart for studies of extracellular remodelling processes, in order to aid the identification of a discrete PAS activation phenotype.

Methods

The PubMed and Web of Science databases were searched for review articles written in the last 5 years, either originally or translated into Polish or English, with the following key:

((Gene) AND (regulation) AND (expression) AND ((uPA) OR (Plasminogen Activating System) OR (tPA) OR (PAI1) OR (uPAR)))

The results were arranged in groups of the memebr of the PAS complex, and the signalling pathway as well as the effect were collated.

Results

35 articles were identified by the strategy, of which 11 were relevant to the topic. A summary is available in Table I, detailing the specific areas present in current literature.

Table 1. Synthesis of PAS genetic activation pathways reviewed within the last 5 years. Seven of the eleven reviews focused on Fibrotic pathologies and investigated PAS elements in light of their pathological involvement. Two focused on vascular diseases, and the remaining two on cancer

Signaling molecules	Transcription factors	PAS Products	Reference
TGF-β	p53-SMAD3 complex	+ PAI-1	(53–58)
	c-Src mediated inhibition RhoA/ ROCK and PPM1A	+ PAI-1	(56)
	Ha-Ras/ERK1,2 MAPK, Rac1/ROS/ NFκB, and Smad3 with co-activator Sky interacting protein (SKIP)	+ uPA	(57,59–61)
Kinins	Unspecified	+ tPA	(62)
Circadian rhythm dependent molecules	CLOCK/BMAL1 and CLOCK/BMAL2	+ PAI-1 - tPA	(63,64)

Conclusions

There is no data regarding uPAR or PAI-2, leading to a lack of a comprehensive map, and there are no alternative pathways identified for uPA tPA, with only PAI-1 having a broad analysis.

There has been little encyclopaedic work done within the last 5 years to bring modern methods of quantitative and qualitative genetic analysis to the forefront of research in to proteolytic degenerative conditions. The prevailing theme of selective investigation and conflicting results within modern lab results calls for a standardisation of protocols which investigate the PAS family, due to their multiple signaling routes and convergent factors.

The current data in the field suggest a higher multitude of discrete stable modes of activation and cross activation of PAS transcription. Further assessment of mechanisms of secretion and recycling could provide a more comprehensive overview of the PAS cycle. Alternatively, a transverse analysis of the data published since the conception of PAS entities over the last half a century could prove invaluable to clarify the intricacies of the PAS interactions which pose problems in studying modern pathologies.

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Conflict of interest statement

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