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Minireview

Role of RIP140 in metabolic tissues: Connections to disease

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Abstract The control of physiological processes requires the regulation and coordination of many different signals and is determined in part by the activation and repression of expression of specific target genes. RIP140 is a ligand dependent coregulator of many nuclear receptors that influence such diverse processes as muscle metabolism, adipocyte and hepatocyte function, and reproduction. Recent evidence has shown that the ability of RIP140 to regulate nuclear receptor function is determined by the relative level of RIP140 expression in comparison with other cofactors, by post-translational modifications and by interactions with additional transcription factors. As a result it is becoming apparent that RIP140, via its interplay with other coregulators, plays a fundamental role in determining both the normal and pathogenic physiological state.

Keywords: Nuclear receptor; Coregulator; RIP140; Metabolism; PGC-1

1. Introduction

Nuclear receptors form a large superfamily of transcription factors, many of which have an important role in regulating the expression of gene networks that control metabolic processes [1–3]. A role for nuclear receptors in metabolism has been determined in part through the identification of dietary-related lipids as receptor ligands [4] and through the development of model systems by genetic modification. These studies have shown that nuclear receptors are involved in the regulation of energy homeostasis [5–7], either through their direct effects in metabolic tissues or indirectly via systemic signalling pathways involving peripheral tissues or the central nervous system. The ability of the receptors to integrate and regulate metabolic pathways is largely determined by cofactors that are capable of remodelling the state of chromatin in the vicinity of target genes and modulating the function of the basic transcription machinery. These cofactors or coregulators form a large, diverse and growing group that are emerging as important factors through which multiple signals converge to regulate specific cellular processes [8,9]. This is particularly the case in metabolic tissues where the expression of coregulators, their binding to nuclear receptors and their activity is determined by a combination of intrinsic factors such as intracellular metabolites that act directly as ligands and extrinsic stimuli acting on cell surface receptors to trigger downstream signalling pathways. For example, alterations in physical activity, stress, body temperature and nutritional status can result in the activation of distinct kinase cascades that induce post-translational modifications. It is primarily through the development of null mouse models however that coregulators such as PGC-1α [6,10], PGC-1β [7], the p160 coactivators SRC-1 (NcoA-1/p160), SRC-2(TIF2/GRIP1/NcoA-2) and SRC-3(pCIP/RAC3/ACTR/pCIP/AIB1/TRAM1) [11–14] and RIP140 [15] have been identified as important controlling factors in metabolism which act as a second level of regulation compared to nuclear receptors.

Gene transcription is a highly regulated process which involves the recruitment and activity of multiprotein complexes and the coordination and integration of many different signals. The global identification of target genes for specific nuclear receptors and cofactors such as RIP140 is beginning to provide important evidence that shows how diverse signalling pathways are coordinated with regard to the control of gene expression. In addition, a number of recent studies have identified coregulators, in the form of both coactivators and corepressors, as important intermediary factors essential for the normal activity of nuclear receptors in physiological processes. This review will focus primarily on new evidence for the developing concept of a fundamental role for RIP140 in normal cellular function as well as in the pathology of metabolic tissues.

2. Identification and tissue specific expression of RIP140

RIP140 was first identified and characterised as a hormone dependent estrogen receptor interacting protein that was also induced by estrogen treatment of breast cancer cells [16,17]. These initial studies indicated that alterations in the relative level of expression of RIP140 could modulate the activity of the estrogen receptor in heterologous cells to result in either activation or repression of transcription of transiently transfected target genes. In particular, at high levels of expression, repression by RIP140 was hormone dependent and required the presence of an intact receptor ligand binding domain.

The RIP140 gene is widely expressed but localised to specific cell types within different tissues. This is particularly apparent in the ovary where expression is highly temporally and hormonally regulated during folliculogenesis and during pregnancy [18,19]. In common with the high degree of primary amino acid sequence conservation between species, the

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organisation of the RIP140 gene (Nrip1) is also very highly conserved. In particular the entire open reading frame (1161 amino acids in mouse, 1158 amino acids in human) is contained within a large exon of approximately 7.3 kb. The highest levels of RIP140 expression however are found in metabolic tissues, notably adipose tissue, liver and muscle [15]. Analysis of skeletal muscle indicates that RIP140 is expressed in a fibre type specific manner with low expression in muscles that are rich in oxidative 'slow-twitch' fibres such as the soleus or the diaphragm and relatively high levels of expression in muscles that are rich in glycolytic 'fast-twitch' fibres such as gastrocnemius and extensor digitorum longus [20]. The mouse RIP140 gene is localised on chromosome 16 (human chromosome 21) [21] and is transcribed from multiple promoters with the major initiation site approximately 100 kb from the single coding exon [22]. Depending on the cell type, expression may be regulated by a variety of hormones including estrogens [23], retinoic acid [24], progestins [25] and vitamin D [26]. In adipogenesis in differentiating 3T3-L1 cells, the gene is transcribed predominantly from exon 1b, also termed the P2 promoter [22]. Expression studies and chromatin immunoprecipitation experiments indicate that the orphan receptor ERRα stimulates transcription from this promoter by two mechanisms, directly by binding to an ERE/ERRE at −650/−633 and indirectly through Sp1 binding sites near to the site of transcriptional activation. Studies in breast cancer cells have identified a number of proximal and distal ERE elements which, in response to estrogen stimulation, result in autoregulatory control of RIP140 expression [27,28]. In general therefore the processes and mechanisms that regulate the levels of RIP140 in metabolic tissues seem to enable a controlled and stable pattern of expression to be maintained in differentiated cells.

In view of the complexity of its expression pattern, post-translational regulation and the variety of transcription factor targets it is perhaps not surprising that RIP140 has pleotropic physiological effects. The identification and characterisation of the roles of RIP140 has become apparent from the development of a RIP140 null mouse model which has provided important insights into the role and function of RIP140 in a number of physiological processes. The demonstration that RIP140 null mice are viable indicates that expression is not essential for development, in contrast with other well characterised nuclear receptor corepressors such as NCoR [29]. In RIP140 null mice however, a variety of different phenotypic changes occur in specific tissues that result in major physiological consequences. Interestingly in some tissues, such as skeletal muscle and the ovary the effects seems to be highly dependent on the relative levels of RIP140 expression, as shown by the intermediate phenotypes in heterozygous animals[18,20]; while in others, such as adipose, this is much less apparent. Whether this dosage effect relates directly or indirectly from tissue specific differences in target gene expression is currently unknown. Interestingly, no related transcripts to RIP140 have been identified by genome sequencing, however a second ligand dependent coregulator termed LCoR has been described which has some similar functional properties, in particular its recruitment to and repression of many nuclear receptors [30]. As yet the possibility of functional compensation between RIP140 and LCoR is still unclear.

A number studies carried out in different laboratories have demonstrated that RIP140 can repress the activity of many, if not all nuclear receptors, including some orphan receptors, and that in some cases repression can occur in the absence of added ligand [31,32]. RIP140 has also been identified as an activator of reporter gene expression when coexpressed with the AhR [33] or with other transcription factors including for example AP1 or Sp1, the latter in combination with ERR isoforms and dependent on the organisation of the target gene promoter [34,35]. Recent studies have also identified a role for RIP140 as an activator of specific networks of genes in the liver [36].

3. Functional properties and mechanism of action of RIP140

The recruitment of RIP140 to nuclear receptors is mediated by LXXLL motifs (where L is leucine and X is any amino acid), alternatively termed NR boxes. There are nine motifs in RIP140 [37] and a 10th LYYML motif (where Y is tyrosine and M is methionine) at the C-terminus of the protein which seems to bind selectively to both retinoid receptors [38] and to LXRβ [39]. All 10 motifs are highly conserved between species in both their primary sequence and position. The presence of a relatively high number of NR-interaction motifs in RIP140 in comparison to other LXXLL containing coregulator proteins may allow some functional redundancy in the interaction of RIP140 with different classes of receptor. Studies have shown that certain NRs have a clear preference for specific RIP140 NR boxes [40–42]. Similarly small fragments of RIP140 can interact in either a ligand dependent or ligand independent way with a particular NRs [43] and in addition to sequence specificity of each motif, mechanisms such as the level of expression of RIP140 or post-translational modifications may also modulate these interactions.

RIP140 seems to function primarily as a scaffold protein that links nuclear receptors to chromatin remodelling enzymes involved in chromatin condensation and transcriptional repression. Four distinct repression domains (RDs) have been identified in RIP140 [44] that may act as binding sites for different repressive enzymatic complexes. The mechanism of repression for both RD1 and RD2 involves recruitment of HDAC modifying enzymes [45] however RD3 and RD4 are yet to be fully characterised.

The repressive function of RIP140 can be modulated by post-translational modifications which include phosphorylation on up to 11 different residues, the functional consequences of which are increased HDAC3 recruitment leading to enhanced repression [46]. Conversely, the biological activity of the corepressor is inhibited by arginine methylation [47]. Modifications have also been identified on lysine residues, one of which is the novel lysine 613 conjugation of pyridoxal 5′-phosphate, the biologically active form of vitamin B6, that results in enhanced repressive activity [48]. Nine lysines have been identified in RIP140 that may be targets for acetylation one of which, (lysine 446) when acetylated prevents recruitment of an additional transcriptional repressor protein, C-terminal binding protein (CtBP) [49]. This specific site is within the RD2 repression domain. In total, four motifs that facilitate CtBP recruitment have been identified in RIP140. Two of these, PIDLS [44,49,50] and PINLS [44,50] are required for repression by RD2. A summary of the functional domains and sites of post translational modification in RIP140 is shown

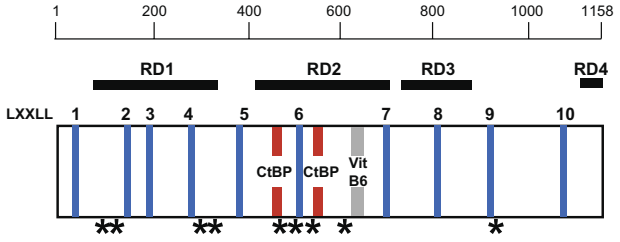

Fig. 1. Functional domains and sites of post translational modification of RIP140. The scale bar indicates the size of the human RIP140 protein in terms of amino acid sequence. LXXLL motifs and the LXXML motif are shown in blue labelled (1–10). Positions of the 4 repression domains RD1–RD4 are marked. Stars indicate positions of potential sites of lysine acetylation and the vertical bars show positions of the interaction sites for CtBP and for covalent modification by vitamin B6. The protein contains approximately 15% serine/threonine residues and sites identified as phosphorylation targets are omitted for clarity.

in Fig. 1. Mechanistically, RD2 acts primarily by HDAC recruitment mediated by the binding of CtBP. This may be partially relieved by the HDAC inhibitor TSA suggesting that CtBP is acting via HDAC-dependent and independent mechanisms.

CtBP is a dehydrogenase that has also been shown to function as a redox sensor in that changes in NADH/NAD^+ ratio may affect its repressive function [51–53]. Large changes in cellular redox state occur in certain metabolic abnormalities, such as diabetes, and alterations in the intracellular redox status by increasing the concentration of NAD(P)H are reported to reduce the amount of abdominal adipose tissue [54,55]. Thus, the repressive activity of RIP140 may be subject to fluctuations in cellular redox potential mediated by CtBP.

4. Identification of target genes and a role for RIP140 in metabolism

The comparison of gene expression profiles from normal tissue and cells with RIP140 null tissues and cell lines has identified many potential target genes that are regulated by RIP140 expression. Analysis of ovarian, adipose and muscle gene expression profiles from wild-type and RIP140 null mice obtained from Affymetrix DNA microarrays has identified changes in gene networks and possible rate-limiting factors important for tissue specific and metabolic changes. Analysis of the microarray data has shown that although RIP140 has been shown to function primarily as a corepressor for nuclear receptors the overall number of genes that were up-regulated in the absence of RIP140 was very similar to the total number of down-regulated genes in all cases [20,32]. In contrast, cluster analysis of genes ascribed to specific metabolic pathways in both adipose tissue and muscle demonstrated that 33% of genes were upregulated and only 4% were downregulated, consistent with the function of RIP140 as a corepressor. The vast majority of upregulated genes in both adipose and muscle were involved in catabolic pathways including fatty acid oxidation, oxidative phosphorylation, glycolysis, and the tricarboxylic acid cycle with many of the upregulated genes common to both tissue types [20,32,56].

Interestingly in this metabolic pathway gene cluster analysis the expression of only seven genes in WAT and five genes in muscle were downregulated in the absence of RIP140 and includes genes which are involved in anabolic pathways, in particular fatty acid and triglyceride synthesis. The expression profiling studies in adipocytes and muscle tissue also revealed increased expression of genes involved in mitochondrial biogenesis and activity in the absence of RIP140. In particular in adipose tissue and cultured adipocytes a number of genes which are normally restricted to expression in brown adipocytes are markedly derepressed in white adipose tissue. An example of this is the gene coding for the mitochondrial uncoupler UCP1. Consistent with all these changes in gene expression adipocytes depleted of RIP140 show elevated oxygen consumption, fatty acid β-oxidation and insulin stimulated glucose uptake [32,56].

Skeletal muscle in both mouse and humans contains distinct types of fibres that are characterized by the expression of specific myosin heavy chain isoforms. Thus different skeletal muscles are adapted for different types of contractile function according to the fibre types they contain. Type I fibres, also known as slow twitch fibres, are rich in mitochondria and exhibit high levels of oxidative phosphorylation making them resistant to fatigue. Type II, or fast twitch fibres, contain a reduced number of mitochondria and rely more on anaerobic respiration via glycolysis or glycogenolysis to enable them to undergo rapid, short contractile bursts. Thus in comparison to type I fibres, type II fibres are more prone to fatigue [57]. There is also an intermediate type of muscle fibre, termed type IIX, that has fast twitch characteristics, but depends on a level of oxidative metabolism that is similar to type I fibres [58]. In response to environmental factors such as for example an increase in load or exercise fibre types can switch, as shown by the appearance of oxidative type I fibres. This switch in fibre type is reflected in changes in the expression of myosin isoforms and other fibre type markers and is accompanied by increased expression of genes involved in mitochondrial biogenesis, fatty acid oxidation and oxidative phosphorylation.

In RIP140 null mice the EDL and gastrocnemius, muscles that normally express relatively high levels of RIP140, exhibit a change to contain more oxidative fibres appearing redder in colour and expressing elevated levels of type I markers. These changes are accompanied by increased mitochondrial number which is coordinated with an up regulation of genes involved in oxidative metabolism, most notably fatty acid oxidation [20]. In contrast, muscles that consist of predominantly type I fibres that normally express low levels of RIP140 show a largely unaltered phenotype in the RIP140 null mice. The importance of the expression level of RIP140 as a major determining factor in muscle physiology is demonstrated by the observation that over expression of RIP140 in muscle results in a reduction in oxidative fibres and an increase in glycolytic markers [20]. This suggests that in common with adipose tissue, RIP140 functions to repress oxidative metabolism and mitochondrial function in skeletal muscle.

5. Nuclear receptor targets of RIP140 and cofactor interplay

An important characteristic of many metabolic genes is that they are transcribed at a basal level yet can be readily activated or repressed in relation to the nutritional or physiological

state. The identification of RIP140 as a key factor in the regulation of metabolic gene expression and mitochondrial function has identified it as a coregulator that shares a number of features in common with the PGC-1 family of polypeptides. In particular there is a remarkable similarity between RIP140 and PGC-1α and PGC-1β target genes, with RIP140 primarily repressing and the PGC-1 cofactors activating, suggesting a functional interplay between these coregulators which is an integral part in the regulation of metabolic processes. In brown adipocytes Ucp1 expression, which is a critical component of the adaptive thermogenic response [59], is largely dependent on PGC-1α activity with this coactivator acting as a focus for signals from different sources. In addition to extracellular stimuli a number of nuclear receptors that are PGC-1a targets are implicated in the regulation of expression of Ucp1 [60], including PPARγ and PPARα, TRs, RXRs and ERRα [61]. The derepression of Ucp1 expression in adipocytes in the absence of RIP140, the enhanced response to different ligands, together with the observation that RIP140 is localised on the Ucp1 enhancer demonstrates that this gene is a common target for both coregulators.

In skeletal muscle the expression of genes involved in mitochondrial function and oxidative phosphorylation is elevated in type I fibres compared with type II fibres. Many of these genes has been shown to be targets for the nuclear receptors PPARδ [62] and ERRα, with the latter acting in part by activating PPARα [63]. There is also a major role for PPARδ, in regulating fibre type switching as shown by expression of a constitutively transcriptionally active form of this receptor resulting in an increase in type I fibres and an associated increase in endurance [62].

The PGC-1 coactivators have been shown to be important factors in the transition of muscle fibre type. PGC1α expression in skeletal muscle varies according to fibre type with higher levels in slow twitch type I muscles such as the soleus muscle, and lower levels in type II muscles such as extensor digitorum longus [64]. Muscle specific expression of PGC-1α in transgenic mice at a level at which this coactivator, in type II fibres, is similar to that normally found in type I fibres, has been shown to be sufficient to switch type II fibres to type I and increase expression of mitochondrial genes to result in resistance to fatigue [64]. Exercise training is also known to induce a switch to greater type I fibres within skeletal muscle and this could be explained by enhanced PGC-1α expression induced by exercise that results in an induction of mitochondrial genes such as cytochrome *c* [65]. In agreement with these observations, one line of PGC1α null mice show reduced mass of typical slow twitch type I muscles with a preservation of type II fibres [6]. This is accompanied by a reduction in mitochondrial number and expression of mitochondrial genes in muscle and a reduced capacity to sustain exercise. PGC-1β is also expressed in muscle, and transgenic mice overexpressing PGC-1β exhibit increased mitochondrial biogenesis and show induction of type IIX oxidative fast twitch fibres [66]. PGC-1β null mice have reduced mitochondrial mass in the soleus muscle [7] thus PGC1β seems to promote the formation of oxidative type IIX fibres. The PGC-1 coactivators are involved in the control of expression of many key muscle metabolic genes which are targeted by nuclear receptors, for example ERRα or PPARδ, or by muscle specific transcription factors such as MEF2D [9]. In muscle cells RIP140 also targets the promoters of PPARδ target genes such as MCAD and the ERRα target gene FABP3 [20]. The discovery of alternative roles for RIP140 and PGC-1 in the regulation of expression of specific genes together with the identification of similar nuclear receptors as potential targets suggests an important functional interplay between these coregulators.

In addition to adipose and muscle tissue, PGC-1α and β have been demonstrated to be important regulators of liver function; however a detailed analysis of the relative importance of each PGC-1 isoform in this tissue and the identification and analysis of the mechanisms of action are still an open question. PGC-1α is not required for lipogenesis but is an important regulator of gluconeogenesis and hepatic lipoprotein metabolism and is also an important factor for many aspects of the response to fasting. In contrast, PGC-1β has no significant effect on gluconeogenesis but has been reported to increase lipogenesis and lipoprotein transport while PGC1βKO mice show lipid accumulation in the liver and a decrease in plasma triglyceride-rich VLDL lipoproteins when fed a high fat diet [7]. A number of nuclear receptors and other transcription factors have been described to be involved in the recruitment of PGC-1 to target genes in liver cells [67] including HNF4α, LXR, PPARα, SREBP1c, CREB, FOXO1 and FOXA2, although in many cases only a subset of genes for any one factor is subject to induction by the coactivators. Recent studies have now identified a hepatocyte specific role for RIP140 as a cofactor for LXR in different ways, namely serving as a coactivator in lipogenesis and as a corepressor in gluconeogenesis [36]. In common with the complex effects of PGC-1 in hepatocytes, RIP140 also acts on a subset of genes in each of these processes, for example, both PEPCK and G6Pase levels are decreased in normal mice when treated with an LXR agonist (T0901317) but PEPCK repression is not maintained in RIP140 null mice. Similarly the repression of PEPCK gene expression by LXR is dependent on RIP140 in hepatocytes in culture while expression of G6Pase is unaffected. These studies, in line with those in cultured adipose and muscle cells demonstrate an intrinsic effect of RIP140 in each specific cell type and therefore suggest that RIP140 has an important role in cell physiology. A list of genes identified as direct targets for RIP140 by chromatin immunoprecipitation is shown in Table 1.

6. Is RIP140 a metabolic counterbalance?

The evidence emerging from both in vivo studies and cellular systems has identified a role for RIP140 as an important regulatory factor in many metabolic processes. In particular the types of genes which are now shown to be RIP140 targets, their regulation by specific nuclear receptors such as ERRα and the PPARs known to be key factors in metabolic tissues combined with the opposing effects of RIP140 and the PGC-1 cofactors suggests that RIP140 can function as a counterbalance in the regulation of metabolism by coregulators. In addition to the control of expression of key enzymes or markers of differentiated cells such as Ucp1 in adipose tissue and specific myosin isoforms in muscle; one of the most fundamental results from the current studies is the identification of a role for RIP140 in mitochondrial function. Whether RIP140 primarily affects basal mitochondrial activity, adaptive mitochondrial responses, or both of these processes is still to be

Table 1
Genes identified as direct targets of RIP140

Tissue/cell type	Gene	Nuclear receptor/ transcription factor	Reference
Adipose/adipocytes	ucp1	PPARs, ERRα	[32]
Myocytes	fabp3	PPARδ	[20]
	mcad	ERRα	[20]
HuH7 hepatocytes	*FAS*	LXR	[36]
FAO hepatocytes	pepck	LXR	[36]
MCF-7 cells	*TMC4*	ER/ AP1	[28]
	IRX4	ER/AP1	[28]
	GUSB	ER/AP1	[28]
	MUC1	ER/AP1	[28]
	C10ORF18	ER/AP1	[28]
LNCaP	*PSA*	AR	[73]
Hela	*MAO-B*	ER/ERR	[74]
H295R human adrenocortical cells	CYP17	SF1	[75]

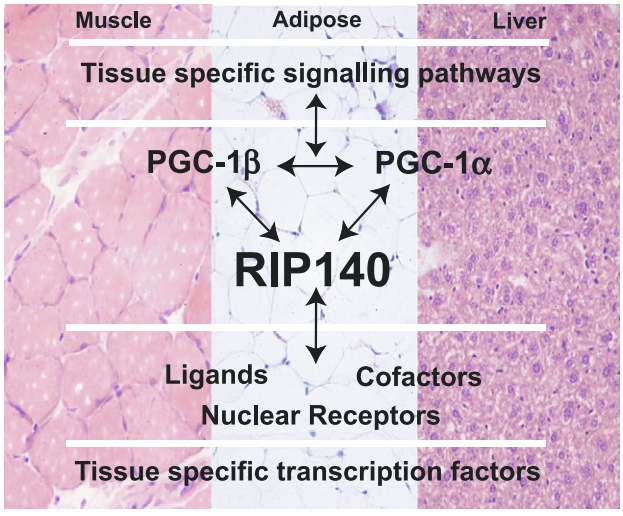

Fig. 2. Model for a central role for RIP140 and in the function of metabolic tissues. RIP140 acts as a counterbalance to control basal and regulated metabolic activity, mainly through functional interplay with PGC-1α and PGC-1β. Gene targets for RIP140 in metabolic tissues are determined primarily by nuclear receptors and are dependent on ligands in addition to other nuclear receptor cofactors. The action of these coregulator pathways is also subject to the effects of other tissue specific signalling pathways and through interactions with tissue specific transcription factors.

determined. Analysis of the affect of altering the level of RIP140 is further complicated due to the compensatory roles of the different PGC-1 coregulators combined with tissue specific factors and signals (Fig. 2). Whatever the precise details of the mechanisms involved, it is clear that RIP140 is an important factor in energy homeostasis.

7. RIP140 and connections to disease

One of the major determining factors in the development of metabolic disorders is abnormal energy expenditure. It is probable therefore that a number of coregulatory factors such as RIP140, PGC-1α and β and the p160 proteins SRC1-3, via their ability to repress or activate anabolic and catabolic functions, may act as important elements in the progression of disease. It is perhaps surprising therefore that as yet there is relatively little evidence for a role for RIP140 in health and disease. RIP140 null mice do not show evidence of lipodystrophy and exhibit normal insulin sensitivity when fed a high fat diet. They are also protected from the development of insulin resistance induced by either aging or high fat feeding, however it is as yet unclear to what extent the loss of RIP140 in muscle, adipose, liver or other tissues plays in terms of whole animal physiology. Nuclear receptors have now been shown to be important targets for drugs to treat diabetes and associated aspects of the metabolic syndrome. The fibrate class of drugs used to treat dyslipidaemia have been found to be potent PPARα ligands [68] and the thiozolinodione (TZD) class used to treat type 2 diabetes (Rosiglitazone and Pioglitazone) function as PPARγ agonists [69]. TZDs have been shown to improve insulin sensitivity and lower blood glucose levels in type 2 diabetes. In murine white adipocytes, the induction of UCP-1 expression following treatment with rosiglitazone is dramatically increased by the depletion of RIP140 [61] suggesting that RIP140 may inhibit the effects of PPARγ ligands to induce expression of genes associated with energy expenditure. The PPARγ ligand pioglitazone, when given to human subjects with type 2 diabetes, increases mitochondrial number in adipose tissue and the expression of many genes associated with oxidative metabolism such as MCAD and CPT1 as well as UCP-1, perhaps mediated via an increase in PGC1α expression [70]. In support of these findings rosiglitazone treatment increases UCP-1 expression in white adipocytes when PGC1α is overexpressed [71]. Despite these changes in gene expression, which might be predicted to increase energy expenditure both pioglitazone and rosiglitazone increase body weight, in part through an expansion of adipose tissue. Several combined PPAR α and γ ligands have also been developed to treat multiple aspects of the metabolic syndrome and diabetes [72] however the clinical outcomes of using these drugs have also not always been as expected. It is conceivable that some of the complex effects of treatment with PPAR ligands may be explained by the effects these agents have on differential recruitment of co-activators or co-repressors to the receptor following ligand binding.

It is interesting to speculate that the lack of a clear association of RIP140 with disease may be a consequence of the pleotropic nature of RIP140. Overexpression of RIP140 or factors that lead to an increase in activity of RIP140 would be predicted to impair mitochondrial function and in a coregulator-counterbalance model this would be compensated for by an increase in the activity of other coregulators such as the PGC-1 family. Loss of function of RIP140 however, although not deleterious as shown by the RIP140 null mouse model, would result in complete infertility and hence any genetic link to health or the incidence of disease unlikely to occur. Clearly while coactivators such as PGC-1a can be induced or regulated in response to metabolic demand it is essential that basal metabolic function is also carefully controlled to maintain normal cell function.

8. Conclusions and future studies

It is emerging that transcriptional coregulator proteins provide an important level of control in a number of metabolic processes. RIP140, via its ligand dependent association with

nuclear receptors, may therefore provide an important target for intervention in the control and regulation of metabolic dysfunction. An integral part of this process will be the identification of natural and synthetic ligands that allow specific or temporal recruitment of coactivators or corepressors such as RIP140 to nuclear receptors. Further studies will be necessary to determine the relative importance of RIP140 expression versus post-translational modifications in specific cell types such as muscle, liver and adipocytes. In addition further analysis of tissue specific signalling pathways will be required, as these may account for the intermediate phenotypes shown in certain types of tissue. It may also be relevant to recall that RIP140 was originally identified as a regulator of estrogen action in breast cancer cell lines and therefore may play a role in metabolic activity in tumour cells and therefore potentially in the growth or progression of hormone dependent tumours. Finally in view of the fundamental role of RIP140 in mitochondrial activity it will be important to determine the role of RIP140 signalling in the function of other cell types such as macrophages and neural cells in which metabolic dysfunction has been shown to be an important factor in the development of disease.

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