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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