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Review

p130Cas: A key signalling node in health and disease

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ABSTRACT

p130Cas/breast cancer anti-oestrogen resistance 1 (BCAR1) is a member of the Cas (Crk-associated substrate) family of adaptor proteins, which have emerged as key signalling nodes capable of interactions with multiple proteins, with important regulatory roles in normal and pathological cell function. The Cas family of proteins is characterised by the presence of multiple conserved motifs for protein–protein interactions, and by extensive tyrosine and serine phosphorylations. Recent studies show that p130Cas contributes to migration, cell cycle control and apoptosis. p130Cas is essential during early embryogenesis, with a critical role in cardiovascular development. Furthermore, p130Cas has been reported to be involved in the development and progression of several human cancers. p130Cas is able to perform roles in multiple processes due to its capacity to regulate a diverse array of signalling pathways, transducing signals from growth factor receptor tyrosine kinases, non-receptor tyrosine kinases, and integrins. In this review we summarise the current understanding of the structure, function, and regulation of p130Cas, and discuss the importance of p130Cas in both physiological and pathophysiological settings, with a focus on the cardiovascular system and cancer.

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1. Introduction

Members of the Cas (Crk-associated substrate) family of adaptor proteins have emerged as highly connected signalling nodes, with important regulatory roles in normal and pathological cell functions. The Cas family of proteins is characterised by the presence of multiple conserved motifs for protein–protein interactions, and by extensive tyrosine and serine phosphorylations. Since the discovery of p130Cas/breast cancer anti-oestrogen resistance 1 (BCAR1) in 1991, three further members of the Cas protein family have been identified: NEDD9 (neural precursor cell expressed, developmentally down-regulated 9; also called human enhancer of filamentation 1 [HEF-1] or Cas-L), EFS (embryonal Fyn-associated substrate), and CASS4 (Cas scaffolding protein family member 4) ([1], and reviewed in [2,3]).

In this review we will present an overview of the signalling integrated by the prototypical member of the Cas-family, p130Cas, and its downstream consequences for cellular signalling. We will then examine the diverse and important roles played by p130Cas in a range of physiological and pathophysiological settings including the cardiovascular system, carcinogenesis, and the immune system.

2. Structural features

p130Cas was initially discovered as a 130 kDa protein which is highly tyrosine phosphorylated in cells expressing p47 v-Crk (C10 regulator of kinase) and p60 v-Src (for *sarcoma*) oncoproteins [1]. p130Cas lacks a kinase domain, but contains various protein–protein interaction domains which mediate associations with a number of binding partners (Fig. 1).

The structure of p130Cas indicates that it fulfils a role as an adaptor protein [4]. As shown by Fig. 1a and b, p130Cas possesses an amino (N)-terminal Src-homology 3 domain (SH3) domain, followed by a proline-rich domain and a substrate domain. The substrate domain is comprised of 15 repeats of the YxxP consensus phosphorylation motif for Src family kinases (SFKs). Src-homology 2 (SH2)-domain containing proteins bind phospho-tyrosine residues in this region, recognising their specific YxxP sequence as determined by the three amino acids following the phospho-tyrosine [4]. Signal amplification and diversification are the likely reasons for the repetitive occurrence of YxxP motifs [5]. Following the substrate domain is the serine-rich domain, which forms a four-helix bundle. This acts as a protein-interaction motif, similar to those found in other adhesion-related proteins such as focal adhesion kinase (FAK) and vinculin [6]. The remaining carboxy-terminal sequence contains a bipartite Src-binding domain (residues 681–713) able to bind both the SH2 and SH3 domains of Src [7], but is otherwise poorly structurally defined, containing few predicted defined secondary structural features.

Other adaptor proteins such as DOK1 (downstream of tyrosine kinase 1), Gab (GRB2-associated binding protein) and Frs (fibroblast growth factor receptor substrate), have been noted to have a similar structure to p130Cas, with a structurally defined domain or domains in the N-terminal region, followed by a large C-terminal region with little defined or predicted structure. One interesting current theory for this organisation is known as the "N-terminal folding nucleation" hypothesis. This proposes that during translation, the N-terminus of the nascent protein emerges from the ribosome and adopts its tertiary structure. The subsequently translated disordered C-terminal region is then able to form intramolecular interactions with the folded N-terminus. This results in a more condensed nascent protein, which is less liable to proteolysis and aggregation, and which may be able to translocate more efficiently to its site of action [8].

Numerous motility-related proteins interact with p130Cas, including Crk, FAK, protein tyrosine kinase 2 (PYK2), non-catalytic region of tyrosine kinase adaptor protein (Nck), and Src, implicating p130Cas as a signalling hub in the control of cell motility [4,9–11] (Fig. 1b).

3. Regulation and functions of p130Cas

The role of p130Cas as an adaptor protein suggests that its regulation – via phosphorylation and dephosphorylation – will have wide-ranging downstream consequences. p130Cas has been demonstrated in many studies to play a key role in cell motility, in both chemotaxis to growth factors, and haptotaxis to ECM components, in addition to roles in the control of the cell cycle and apoptosis (reviewed in [12,13]).

The control of p130Cas as a signalling node involves a balance between the activity of kinases and that of tyrosine phosphatases [12–14]. In turn, p130Cas exerts a major role in cell motility via the modulation of small guanine triphosphatase (GTPase) activity, which is central to the control of actin cytoskeleton dynamics. Cell migration requires the spatiotemporal control of signalling events in order to produce coordinated, persistent movement. A typical mesenchymal mode of motility requires a balance of forward protrusion of the cell membrane, and tail retraction via contraction and release of focal contacts. In structural terms, this requires asymmetric organisation of the assembly and disassembly of focal adhesions and stress fibres ([15,16], and reviewed in [17]).

3.1. Tyrosine phosphorylation

Tyrosine phosphorylation is the major post-translational modification of p130Cas, and occurs predominantly in the 15 YxxP repeats within the substrate domain. Tyrosine phosphorylation occurs as a result of a diverse range of extracellular stimuli, including growth factor stimulation [12], integrin activation [18], and peptide hormone ligands for G-protein coupled receptors (GPCRs) [19].

A variety of growth factors induce p130Cas phosphorylation via protein receptor kinase activity, including vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth