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Review

A perspective on non-catalytic Src homology (SH) adaptor signalling proteins

Vikash Reebye [a], Andrea Frilling [a], Amin Hajitou [b], Joanna P. Nicholls [a], Nagy A. Habib [a], Paul J. Mintz [a,*]

[a] Imperial College London, Faculty of Medicine, Department of Surgery and Cancer, London, W12 0NN, UK
[b] Imperial College London, Faculty of Medicine, Division of Experimental Medicine, London, W12 0NN, UK

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ABSTRACT

Intracellular adaptor signalling proteins are members of a large family of mediators crucial for signal transduction pathways. Structurally, these molecules contain one Src Homology 2 (SH2) domain and one or more Src Homology 3 (SH3) domain(s); with either a catalytic subunit, or with other non-catalytic modular subunits. Cells depend on these regulatory signalling molecules to transmit information to the nucleus from both external and internal cues including growth factors, cytokines and steroids. Although there is a vast library of adaptor signalling proteins expressed ubiquitously in cells, the vital role these SH containing proteins play in regulating cellular signalling lacks the recognition they deserve. Their target selection method via the SH domains is simple yet highly effective. The SH3 domain(s) interact with proteins that contain proline-rich motifs, whereas the SH2 domain only binds to proteins containing phosphotyrosine residues. This unique characteristic physically enables proteins from a diverse range of networks to assemble for amplification of a signalling event. The biological consequence generated from these adaptor signalling proteins in a constantly changing microenvironment have profound regulatory effect on cell fate decision particularly when this is involved in the progression of a diseased state.

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1. Introduction

Signal transduction pathways are understandably one of the most important biological mechanisms that regulate molecular and cellular processes including cell cycle control, differentiation, apoptosis, gene expression and development. A disruption of this intricately regulated pathway inevitably leads to undesired outcomes such as uncontrolled cell proliferation and loss of apoptosis. In a clinical setting this leads to tumour growth and progression to metastatic disease [1]. Cellular signal transduction is initiated at multiple levels and involves an orchestrated cascade of events which generally begins with the activation of specialised receptor proteins located either on the cell surface membrane (cell surface receptor signalling) or the cytoplasm, the nuclear membrane and the nucleus (intracellular receptor signalling) [2]. A control mechanism that is inherently accurate comprising of key regulatory proteins then perpetuates this signal transduction according to environmental cues such as fibronectin binding to integrin, growth factors binding to cell surface receptors or steroid hormones binding to nuclear receptors in the cytoplasm (Fig. 1). Once the receptors are activated, intracellular regulatory proteins are recruited to form functional complexes through protein–protein interactions. The assembly of these complexes provides a mechanism to further amplify the signalling process leading to regulation of downstream target genes (Fig. 1).

There are numerous examples of cell signalling events that are mediated via cell surface receptors [2]. The receptor tyrosine kinases (RTK), G-protein-coupled receptors (GPCR) and integrins are the most commonly cited examples that activate the mitogen-activated protein kinase (MAPK) signal transduction pathway [2–4]. During activation of the MAPK pathway, intracellular adaptors and regulatory proteins are recruited and integrated into the signalling process. These adaptor

* Corresponding author.
E-mail address: p.mintz@imperial.ac.uk (P.J. Mintz).

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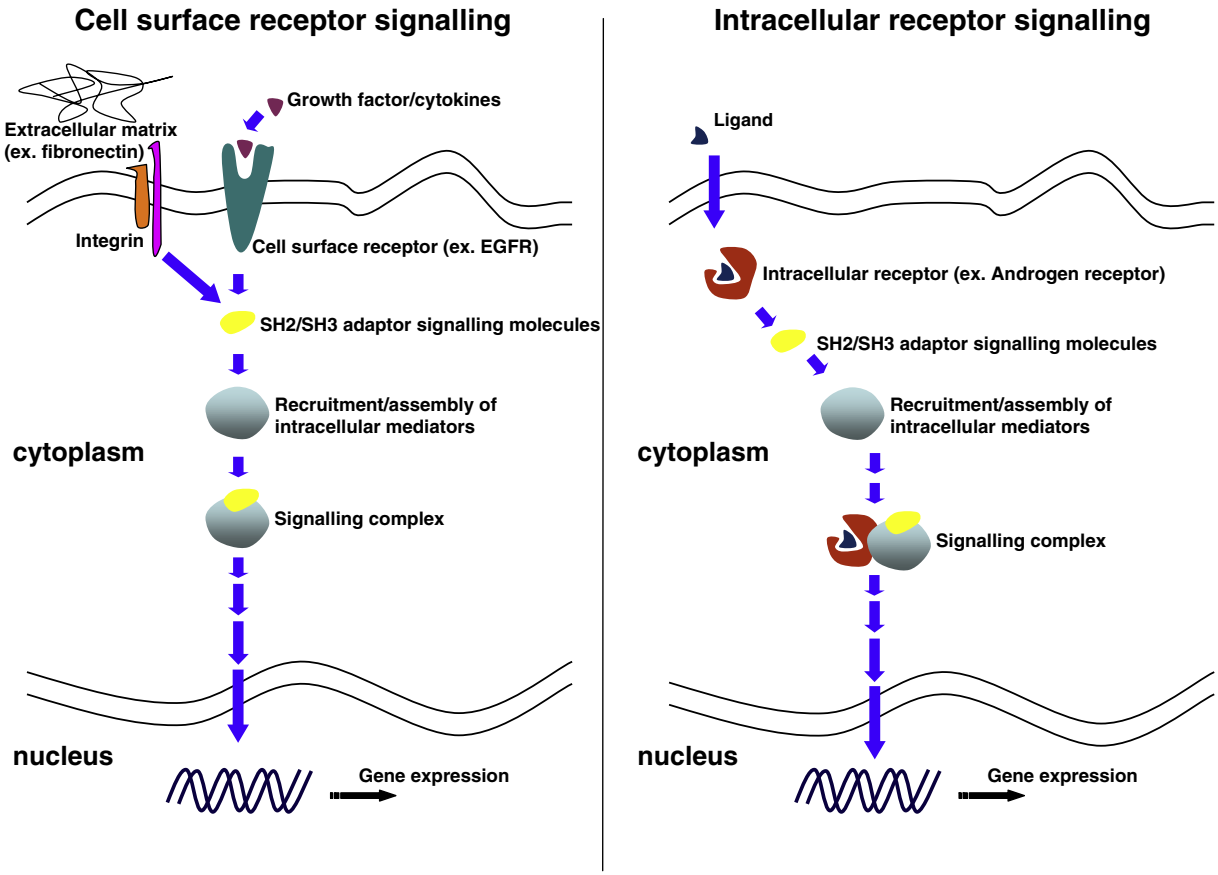

Fig. 1. A schematic diagram of cell receptor signalling. The cell employs two different receptor signalling mechanisms to transmit information to the nucleus in order to modulate gene expression. Cell surface receptor signalling (left panel) such as the EGFR can be initiated by growth factors and cytokines as well as cues from the extracellular matrix such as integrins. Intracellular receptor signalling (right panel) such as the androgen receptor is fully engaged throughout the signalling process and unlike cell surface receptors are more dynamic in function. These two pathways are not mutually exclusive as evidence suggests that they are able to converge through mechanisms as yet not fully defined. The dynamic and complex function of adaptor signalling proteins however makes them an ideal candidate for inducing this cross over between cell surface receptor signalling and intracellular receptor signalling.

molecules include Grb2, CrkL, paxillin, Nck, and DOCK amongst many others that provide the physical bridge to connect subsequent signalling mediators. In addition to cell surface transmembrane receptors cytoplasmic or nuclear receptors are equally important in mediating cell signalling (Fig. 1, right panel). Unlike the anchored attributes of transmembrane receptors, the highly 'mobile' nature of internal receptors ties in with their dynamic roles of mediating both genomic and non-genomic effects. The androgen and glucocorticoid receptors are a good example of this where their genomic effects are largely mediated via specific binding of ligands that directs their translocation directly to the nucleus with the aid of chaperone proteins [5]. Their non-genomic effects however are intimately linked to activation of accessory proteins (including adaptor proteins) bridging the internal receptors to the cell signalling network. The one converging theme that is becoming clearer—as more data is being generated on characterisation of the cell signalling network—is the importance of intracellular adaptor proteins for integrating the cell signalling network to transcriptional regulation [6], and cell fate decision.

There are numerous intracellular proteins that contain the src homology 2 and 3 (SH2 and SH3) domains in addition to other modular domains (Fig. 2). Among these myriad of multidomained intracellular proteins is an evolutionarily conserved class of adaptor signalling proteins associated with the signal transduction pathways that are void of accessory modules. These adaptor proteins only contain a single SH2 and two SH3 domains (Fig. 2, left panel). SH domains are small non catalytic domains (60–100 amino acids) critical for protein–protein interactions [3,7]. SH2 interacts with phosphotyrosine residues, whereas SH3 recognises proline-rich regions. Together, the different combination or permutation of SH2 and SH3 amongst these separate class of adaptor protein, provides a remarkable array of control over intracellular signalling. Their importance has been well documented in various biological and cellular processes including endocytosis, cytoskeletal organisation, proliferation, migration, cell–cell communication, and immune regulation and will be the basis of this review [3,8–10]. Despite the simple structure of CrkL, Grb2 and Nck, their extremely complex functional influence on the cell signalling network and their importance in physically linking key regulatory proteins will be discussed; offering a different perspective on what facilitates the flexibility and adaptability of cell signalling in a constantly changing microenvironment.

2. Grb2

Growth factor receptor-bound protein 2 (Grb2) is a classic example of an adaptor signalling protein that can simultaneously interact with two or more signalling molecules whilst orchestrating the assembly of multiprotein complexes associated with cell surface receptors. These include the epidermal growth factor receptor (EGFR) and platelet-derived growth factor (PDGF) receptor. The structure of Grb2 consists of an SH2 domain flanked by two SH3 domains (Fig. 2, left panel) [11,12]. The crystal structure of its SH2 domain confirms a high binding affinity to activated receptor tyrosine kinases (RTK) such as EGFR whilst its two SH3 domains show binding affinity to proline-rich regions. Together, both SH2 and SH3 domains of Grb2 are responsible for promoting the assembly of multi-protein complexes which can either influence activation or repression of downstream effectors [13]. Upon growth factor stimulation by epidermal growth factor (EGF), a key tyrosine residue on EGFR becomes phosphorylated resulting in the recruitment of