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Review

The role of pseudokinases in cancer

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ABSTRACT

Kinases play a critical role in regulating many cellular functions including development, differentiation and proliferation. To date, over 518 proteins with kinase activity, comprising ~2–3% of total cellular proteins, have been identified from within the human kinome. Interestingly, approximately 10% of kinases are categorised as pseudokinases since they lack one or more conserved catalytic residues within their kinase domain and were originally thought to have no enzymatic activity. Recently, there has been strong evidence to suggest that some pseudokinsases can not only function as scaffold proteins, but may also possess kinase activity leading to modulation of cell signalling pathways. Altered activity of these pseudokinases can result in impaired cellular function, particularly in malignancies. In this review we are discussing recent evidence that apart from a scaffolding role, pseudokinases also orchestrate cellular processes as active kinases *per se* in signalling pathways of malignant cells.

Contents

Abbreviations: ALL, Acute Lymphoblastic Leukaemia; AML, Acute Myeloid Leukaemia; AMPK, 5′-Adenosine Monophosphate Activated Protein Kinase; ATF4, Activating Transcriptional Factor 4; ATP, Adenosine-5′-Triphosphate; BTICs, Brain Tumour-Initiating Cells; C/EBPα, CCAAT/Enhancer-Binding Protein-A; CASK, Ca^{2+}/Calmodulin-Dependent Serine Protein Kinase; CCK4, Colon Carcinoma Kinase 4; C-TAK1, Cdc25C-Associated Kinase 1; EGF, Epidermal Growth Factor; EGFR, EGFR Receptor; ERα, Oestrogen Receptor A; FOXO3a, Forkhead Box O3a; GSK3, Glycogen Synthase Kinase 3; HAT, Histone Acetyltransferase; HER3 (erbB3), Receptor Tyrosine Protein Kinase 3; IL-9, Interleukin-9; ILK, Integrin-Linked Kinase; JAK, Janus Tyrosine Kinase; JNK1, C-Jun Amino Terminal Kinase-1; KSR1, Kinase Suppressor of Ras1; LIM, Lin11, Isl-1 and Mec-3; LKB1, Liver Kinase B1; LOH, Loss of Heterozygosity; MAGUK, Membrane Associated Guanylate Kinase; MAPK, Mitogen-Activated Protein Kinase; MO25α, Mouse Protein 25 A; MT1-MMP, Membrane Type-1 Matrix Metalloproteinase; mTOR, Mammalian Target of Rapamycin; PI3K, Phosphatidylinositol-3-OH Kinase; PIKK, Phosphatidylinositol 3-Kinase-Related Kinase; PJS, Peutz–Jeghers Syndrome; PKA, Protein Kinase A; PP2A, Protein Phosphatase 2A; PRD, PIKK-Regulatory Domain; RTK7, Receptor Tyrosine Kinase 7; STATs, Signal Transducers and Activators of Transcription; STRADα, STE-20-Related Adaptors A; TFF1, Trefoil Factor 1; TGF-β, Transforming Growth Factor-B; TNFα, Tumour Necrosis Factor A; Trb, Tribbles Homolog; TRRAP, Transformation/Transcription Domain-Associated Protein; Tyk2, Tyrosine Kinase 2; VRK-3, Vaccinia-Related Kinase 3.

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1. Introduction

The human kinome accounts for approximately 2% of all genes [1,2] and protein kinases are essential for regulating many cellular functions in both the physiological and pathological context. Kinases have conserved residues necessary for their catalytic activity, by transferring phosphate groups from adenosine-5′-triphosphate (ATP) to specific serine, threonine or tyrosine residue in target proteins. Phosphorylation leads to activation or inhibition, depending on the target substrate, usually resulting in downstream effects involving other proteins. However nearly 10% of known kinases lack one or more of these residues and are classified as pseudokinases therefore becoming catalytically inactive or lacking necessary binding domains. Pseudokinases are randomly distributed on the phylogenetic tree of kinases suggesting that they may have evolved from diverse active kinases. The initial belief that pseudokinases are vestigial remnants of active kinases that primarily act as scaffold proteins is changing. Some of them demonstrate kinase activity while others play critical roles as activators of their specific targets. Aberrant regulation of pseudokinases is implicated in the cause and development of a variety of diseases. In this review, we identify which pseudokinases have been associated with cancer and discuss recent important advances in uncovering their potential roles as therapeutic targets.

2. Pseudokinases: evolutionary counterparts of protein kinases?

The term “pseudokinase” originated from the concept that these protein kinases lack one or more conserved residues that are crucial for enzymatic activities compared to classic protein kinases such as protein kinase A (PKA), and therefore they are not be able to phosphorylate different substrates. Based on sequence analysis, Manning and colleagues [1] showed that approximately 50 protein kinases in the human kinome are classified as pseudokinases, which require the intact three motifs: i) VAIK (Val–Ala–Ile–Lys), ii) HRD (His–Arg–Asp) and iii) DFG (Asp–Phe–Gly) for ATP and peptide binding (Fig. 1) (reviewed by Boudeau and Alessi, Zeqiraj and Aalten [3–5]). Interestingly, it appears that these pseudokinases are widely located in every branch in the phylogenetic tree, which implies from evolutionary perspective that they might function similarly to active protein kinases. Recent structural investigations have provided further evidence to support this hypothesis. For example, the WNK kinase lacking the key lysine (K) residue in the VAIK motif, within the catalytic subdomain II was shown that it can function actively by using another neighbouring lysine in the β strand 2 domain [6,7]. Ca^{2+}/calmodulin-dependent serine protein kinase (CASK) is another good example where despite the absence of key enzymatic residues in the DFG motif, which is indispensable for Mg^{2+} binding, it can still implement itself in a constitutively active conformation, capable of autophosphorylation and for phosphorylating specific substrate such as the synaptic protein neurexin-1. Unlike other kinases that require Mg^{2+} for their function, CASK works independently of Mg^{2+}, which surprisingly inhibits its catalytic activity [8,9]. The elucidation of the crystal structure of the receptor tyrosine protein kinase HER3 (erbB3) challenged the concept that it was an inactive pseudokinase, since it was lacking the intact conserved motif HRD, which is required for phosphorylation. In fact, in order to promote phosphate transfer, HER3 can adopt itself in an active conformation through a unique mechanism by its kinase-defective domain [10,11].

No matter what functions these pseudokinases perform either as scaffold proteins, allosteric regulators or active kinases, emerging

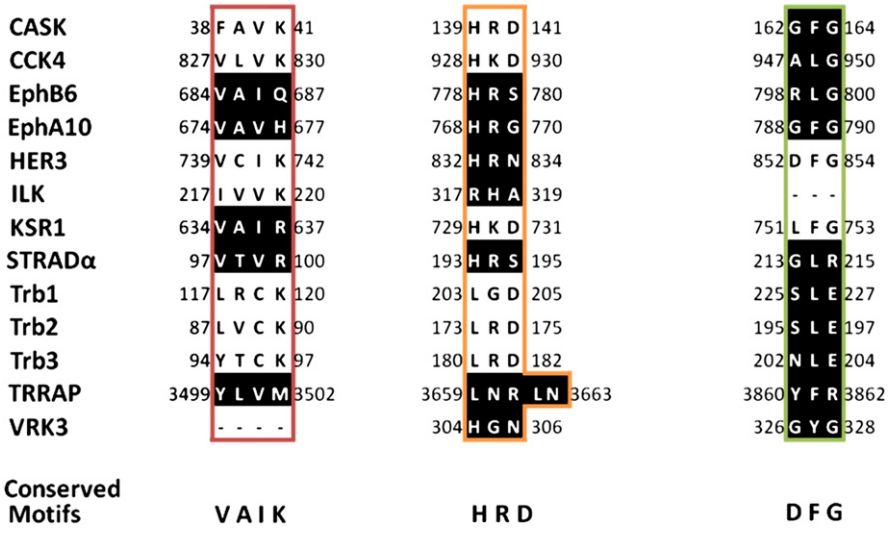

Fig. 1. Multiple sequence alignment of pseudokinases comparing the three conserved motifs (VAIK, HRD and DFG), located within the catalytic domain, which are essential for enzymatic activity. Highlighted in black are the indicated missing motifs for each pseudokinase.