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REVIEW

Oncogenic Signaling Adaptor Proteins

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ABSTRACT

Signal transduction pathways activated by receptor tyrosine kinases (RTK) play a critical role in many aspects of cell function. Adaptor proteins serve an important scaffolding function that facilitates key signaling transduction events downstream of RTKs. Recent work integrating both structural and functional genomic approaches has identified several adaptor proteins as new oncogenes. In this review, we focus on the discovery, structure and function, and therapeutic implication of three of these adaptor oncogenes, *CRKL*, *GAB2*, and *FRS2*. Each of the three genes is recurrently amplified in lung adenocarcinoma or ovarian cancer, and is essential to cancer cell lines that harbor such amplification. Overexpression of each gene is able to transform immortalized human cell lines in *in vitro* or *in vivo* models. These observations identify adaptor protein as a distinct class of oncogenes and potential therapeutic targets.

KEYWORDS: Adaptor protein; Cancer; Oncogene

INTRODUCTION

Receptor tyrosine kinase (RTK) signaling plays key roles in development and cell physiology. Inappropriate activation of these signaling pathways contributes to the genesis and progression of many types of cancer. A prototypical RTK signaling pathway starts with activation by growth factor ligand binding which induces receptor dimerization (Lemmon and Schlessinger, 2010). This dimerization event facilitates the *trans*-phosphorylation of RTKs, which recruits and activates downstream signaling molecules. These signaling molecules may be directly recruited by binding to RTKs, or indirectly recruited by adaptor proteins that form specific complexes with both the signaling molecules and the associated RTKs. Adaptor proteins lack enzymatic activity but provide an important scaffolding function that facilitates key signaling transduction events and regulates signal specificity and amplification (Pawson and Scott, 1997). As such, adaptor proteins exert temporal control over activated signaling pathways by varying expression level and phosphorylation status.

The adaptor proteins are classified into two groups based on structure and function (Gotoh, 2008). First group is comprised of docking proteins that have multiple tyrosine phosphorylation sites to bind downstream signaling proteins. Examples of this group include GRB2-associated binding protein (GAB), fibroblast growth factor receptor substrate 2 (FRS2), insulin receptor substrate (IRS), Src homology 2-containing protein (SHC), and downstream of kinase (DOK)-family proteins (Fig. 1). This group of adaptor proteins often contains membrane localization domains and are also called membrane-linked docking proteins (MLDP). The second group is comprised of adaptor proteins with only Src homology 3 (SH3) and/or SH2 domains to bind signaling proteins, without a membrane localization structure or phosphorylation sites. Examples of the second group include GRB2, CRK, and NCK.

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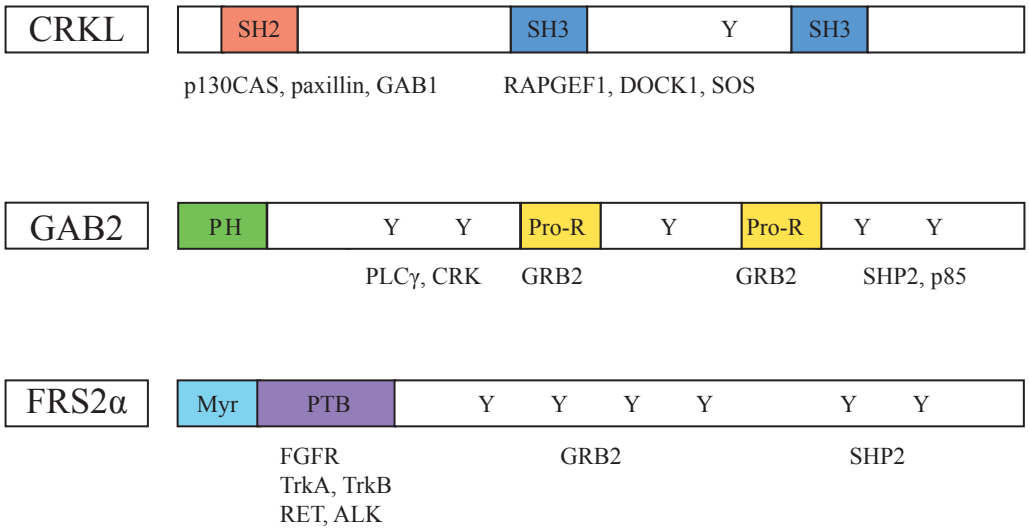

Fig. 1. Schematic representation of CRKL, GAB2, and FRS2α.
The CRKL protein structure contains one SH2 (Src homology 2) domain that binds to p130CAS (also known as BCAR1), paxillin, and GAB1, and two SH3 (Src homology 3) domains (SH3N and SH3C) that interact with RAPGEF1, DOCK1, and SOS. Structural domains of GAB2 include an N-terminal PH (Pleckstrin homology) domain that is critical for membrane localization, and central proline-rich (Pro-R) domains that interact with SH2 and SH3 domain-containing proteins such as GRB2. Multiple phosphorylation sites are also present to bind to signaling partners such as PLC-γ, CRK, SHP2, and p85. FRS2α contains an N-terminal myristoylation site for membrane anchoring, a C-terminal phosphotyrosine binding (PTB) domain that interacts with limited species of receptors. It also includes multiple tyrosine phosphorylation sites that bind to SH2 domains of GRB2 and GAB1.

We and others have shown that several genes encoding adaptor proteins are recurrently amplified in lung adenocarcinomas and primary ovarian cancers and essential to proliferation and survival in cancer cells that harbor those amplifications (Brown et al., 2008; Luo et al., 2008, 2015; Kim et al., 2010; Cheung et al., 2011a, 2011b; Wang et al., 2012; Dunn et al., 2014). Overexpression of these genes in immortalized human cell lines promoted anchorage-independent growth and tumorigenesis. These studies suggest that adaptor protein-encoding genes are oncogenes in a subset of lung adenocarcinomas and ovarian cancers. In this review, we will focus on the discovery, structure and function, and therapeutic implications of *CRKL*, *GAB2*, and *FRS2*.

STRUCTURE AND FUNCTION OF ADAPTOR PROTEINS

The CRK family consists of three members, CRKI, CRKII, and CRK-like protein (CRKL). CRKI and CRKII are alternative transcripts of *CRK*. The CRK family proteins integrate signals from multiple sources (Fig. 2) including growth factor receptors (Birge et al., 2009), integrin receptors (Cabodi et al., 2010), bacterial and viral pathogens (Weidow et al., 2000; Heikkinen et al., 2008), and apoptotic cells (Albert et al., 2000). Examples of the growth factor receptors that mediate signaling through CRK or CRKL include EGFRs, neurotrophin growth factor receptors (TrkA), IGF-R, PDGFRα, VEGFR, Met, and EphB2 receptor (Birge et al., 2009). CRK family also belongs to the category of intracellular integrin signaling adaptor proteins that include the Cas family, the IPP complex, and the Cap family (Cabodi et al., 2010). The integrin receptors, such as β1 integrin receptor, are enzymatically inactive receptors that upon binding the extracellular matrix (ECM), undergo conformational change and initiate signal transduction through intracellular adaptor proteins.

CRKL consists of an N-terminal SH2 domain followed by two SH3 domains (SH2-SH3N-SH3C) (Fig. 1) (Feller, 2001). The SH2 domain of CRKL binds to a specific motif (Y-x-x-P) present within the docking proteins such as p130CAS (also known as BCAR1), paxillin, and GRB2-associated binding protein (GAB). The N-terminal SH3 domain (SH3N) binds to proteins that contain a proline-rich motif (P-x-x-P-x-K), such as Son of Sevenless (SOS), RAPGEF1 (also known as C3G), p85, and BCR-ABL1 (Nichols et al., 1994; Oda et al., 1994; Feller et al., 1995; Sattler et al., 1997). The protein complexes formed by CRKL and these binding partners are important for many biological processes such as cell proliferation, survival, adhesion and migration (Feller, 2001; Birge et al., 2009).

GAB2 belongs to an evolutionary conserved family of three proteins, GAB1, GAB2, and GAB3. Three family members share 40%−50% sequence homology but each member also has unique structural motifs that allow specific signaling to downstream receptors (Gu and Neel, 2003). GAB2 protein contains highly conserved structural motifs that include an N-terminal Pleckstrin homology (PH) domain, central proline-rich domains, and multiple tyrosine residues (Fig. 1) (Gu et al., 1998). The PH domain plays a role in membrane localization of GAB2 through binding to cell membrane phospholipids. The central proline-rich domains serve as a docking site for SH3 domain-containing proteins such as GRB2. GRB2 is the primary upstream regulator of GAB2 and binds to GAB2 through its C-terminal "canonical" (P-x-x-P-x-