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Translational evidence on the role of Src kinase and activated Src kinase in invasive breast cancer

Beatrix Elsberger*

Dundee Cancer Centre, Clinical Research Centre, Ninewells Hospital and Medical School, Dundee DD1 9SY, United Kingdom

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Contents

Abstract

Src kinase is a member of a non-receptor tyrosine kinase family. It has been implicated as a regulator of cell proliferation and survival and plays a complex role in cell adhesion and motility. *In vitro* evidence for a role for Src in breast cancer is compelling. However, only a few translational clinical studies have been undertaken in this field. This review summarises translational evidence on expression and activation of Src kinase in breast cancer patient cohorts exploring clinical significance and the possibility of identifying key biomarkers. There is strengthened translational proof for a definitive role of Src in breast cancer. Nevertheless, there remains a need to find a robust biomarker to identify patients responsive to Src inhibitors for clinical trials.

Keywords: Src kinase; Breast cancer; Translational research; Src kinase inhibitors

1. Background

The Src kinase family (SFK) is a family of non-receptor tyrosine kinases. Src, the most widely known and investigated, is the prototypical member of this eight-strong group of structurally related proteins expressed in mammalian cells. Src family kinases are regulatory proteins, playing key roles in cell differentiation, motility, invasion, proliferation and cell survival [1]. The Src family comprises Blk, Fgr, Fyn, Hck, Lck, Lyn, Src, and Yes (alphabetically listed) [2]. Each SFK member has a different distribution in

* Tel.: +44 1382633936; fax: +44 1382496363.
E-mail address: b.elsberger@nhs.net

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normal tissues. Blk, Hck, and Fgr are found solely within blood cells; Lck and Lyn are found in blood cells and brain; Yes, Fyn and Src are ubiquitously expressed [3].

1.1. Src structure

The three dimensional structure of c-Src is well understood. The Src protein is a 60 kDa tyrosine kinase. It has a N-terminal 14-carbon myristoyl sequence, a SH4 domain, an unique segment, a SH3 and SH2 domain, a protein-tyrosine kinase domain and a short C-terminal regulatory tail (Fig. 1a). The N-terminal myristylation of Src is required for association with cellular membranes and is crucial for the transformation of oncogenic Src mutants [4]. In fibroblasts Src is bound to endosomes, perinuclear membranes, secretory vesicles and the cytoplasmic face of the plasma membrane by its N-terminal myristoyl group [5], where it can interact with a variety of growth factors and integrin receptors [6]. The unique amino-terminal domain varies between Src kinase family members. The four distinct Src-homology (SH1-4) domains are involved in autoregulating Src kinase activity and interacting with substrates to form intracellular signalling complexes [6]. Src activation is dependent on the interaction of different SH domains with each other and a carboxy-terminal (C-terminal) domain.

1.2. Src activation and mechanism

Activation of Src is complicated and can occur in different ways. The classical activation pathway involves dephosphorylation of a negative regulatory domain as well as phosphorylation of an activation loop and/or activation by protein interactions. The c-terminus (Y530 residue on c-Src) binds to SH2 when phosphorylated. Phosphorylation at tyrosine site 530 (Y530) keeps c-Src in a closed configuration (Fig. 1b). Dephosphorylation of Y530 causes a configuration change, displaying the substrate-binding pocket, allowing the kinase access to substrates and leading to phosphorylation of Y419, which is required for full catalytic activity (Fig. 1c) [5]. More recently a different activation pathway has been discovered. Platelet-derived growth factor receptor (PDGF) or human epidermal growth factor receptor 2 (HER2) driven phosphorylation of c-Src at Y215 has been shown to block binding to the c-terminal regulatory sequence and result in a 50-fold activation of Src [7]. In addition to this, the activated PDGFR has been shown to phosphorylate the tyrosine 138 site within the SH3 domain, although the consequences are less clear. Phosphorylation at the tyrosine 138 site has not been shown to be required for Src kinase activation, but may be involved in SH3 domain interactions. Although Src SH3 interactions remain to be fully elucidated, the SH3 domain of the protein has been shown to bind to substrates containing proline-rich regions [8]. The SH2 and SH3 domains can bind to growth factor receptors that contain their own tyrosine kinase activities, including EGFR, HER2, PDGFR, VEGFR and FGFR. The SH2 and SH3 domains can also bind to and activate cytoskeletal proteins such as FAK and p130CAS [2]. This direct interaction with substrates that contain their own tyrosine kinase domains can activate the intrinsic tyrosine kinase activity of Src, potentially altering localisation of Src to sites of action [9].

SFKs can be found at different subcellular locations. They are most abundantly localised in the cell cytoplasm, but are re-localised to the membrane when activated. Subcellular localisation has also been suggested to regulate Src activity [10]. The cellular location of this protein seems to play an

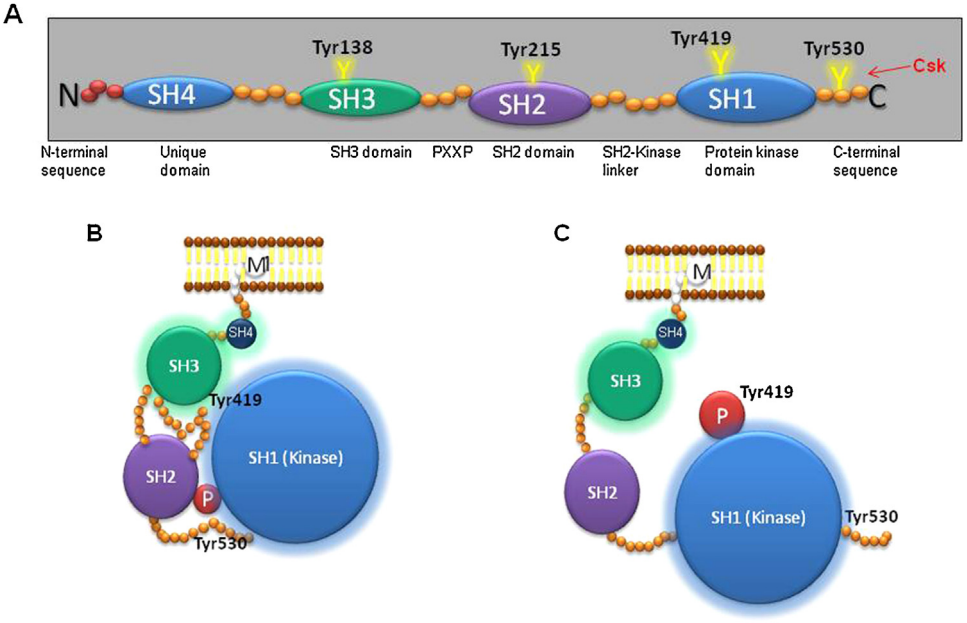

Fig. 1. (A) Illustrates a simplified one dimensional schematic overview of the basic structure of Src. (B) and (C) demonstrate Src kinase configuration when activated via dephosphorylation of Tyr530 and phosphorylation of Tyr419.