Review

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Focal Adhesion Kinase (FAK) and c-Src Dependent Signal Transduction in Cell Adhesion

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This review predominantly acquaints the role of focal adhesion kinase (FAK) and cellular-Src (c-Src) in cell adhesion. Cell adhesion is a crucial phenomenon that causes the cells to interact with the extracellular matrix (ECM) or with each other. There are different proteins involved in cell adhesion including cell adhesion molecules (CAMs)/receptors that are present on the cell surface and various cytoplasmic proteins. FAK and c-Src are two proteins in the cytoplasm, which serve as regulators of different proteins involved in cell adhesion. They activate talin, vinculin and paxillin in turn connect the integrins with the cytoskeleton and in this way strengthen the integrin interaction with ECM. FAK-Src signalling also modulates cell-cell adhesion by regulating actin interactions. Being a key modulator of cell adhesion, FAK and c-Src signalling are linked with different pathological conditions like cancer, cardiovascular diseases, and embryonic developmental disorders. Thus, comprehensive research into FAK-Src signalling is of great importance in the exploration of different signalling targets for therapeutic interpretations. Different inhibitors and antibodies against various cell adhesion proteins, such as FAK, c-Src, and integrins, have already been used in preclinical and clinical trials to treat a variety of diseases, including cancer and chronic inflammatory conditions. Furthermore, this review presents different challenges to FAK-Src and cell adhesion signalling targeted drug development, which include, cytotoxicity and cell resistance to the drug. Finally, this review remarks that FAK and c-Src are important regulators of cell adhesion and are linked to various pathologies, nevertheless, more comprehensive research on these proteins would be a significant step forward in the development of effective therapies for the diseases associated with them.

Keywords: focal adhesion kinase (FAK); cell adhesion molecules (CAMs); c-Src; signal transduction; cell adhesion

Introduction

Cell adhesion is a critical phenomenon in which cells interact with other cells or the extracellular environment in highly regulated ways [1]. In multicellular organisms, cell-to-cell and cell-to-extracellular environment communication is essential for many vital biological phenomena such as cell proliferation, tissue formation, cell differentiation, immune response, cell migration, wound healing, apoptosis and cell survival [2]. In this regard, cell adhesion is of vital importance and is responsible for cell-cell and cell-extracellular matrix (ECM) interactions.

The adhesive interactions in cell adhesion occur due to the presence of different proteins on the cell surface called cell adhesion molecules (CAMs). These adhesion molecules on the cell surface can have strong binding interactions, such as interactions among cells in tissue that maintain the structural integrity of the tissues [3], or weak, dynamic, and transient interactions, such as those between motile white blood cells. These surface cell adhesion proteins include integrins, cadherin, immunoglobulin and other cell surface proteins such as selectins etc, which serve as cell surface signalling receptors in cell adhesion [4,5]. Focal adhesion kinase (FAK) and cellular-Src (c-Src) are two important cytoplasmic proteins, which play an important role in cell adhesion by regulating cell surface adhesion proteins via critical signal transduction pathways [6–8].

FAK was discovered in the early 1990s while investigating integrin-mediated cell adhesion to ECM. In this study, integrins were isolated, along with FAK associated with it, from the cell adhesion site. At the time of its discovery from focal adhesion sites, it was found in phosphorylated form at certain tyrosine residues [9,10]. After its discovery, research on characterization and functions, and its role in cell adhesion was established. Initial research on FAK revealed that it is a non-receptor tyrosine kinase that remains in auto inhibited state in cytoplasm. It is activated by autophosphorylation upon signal reception from ECM by integrin [11]. It was also found that FAK plays an integral role in cell adhesion by recruiting other proteins involved in cytoskeletal rearrangement and cell adhesion [12]. These initial findings led a path to the exploration of the role of the FAK in processes associated with cell adhesion including cell survival, proliferation, migration and apoptosis [13]. It also provided the footprints for the development of therapeutic strategies for different diseases arising from a malfunction in cell adhesion signalling. FAK ac-

tivation is dependent on the strength of the tension applied to focal adhesions. Single focal adhesions with polarized FAK activity that is induced by tension can contribute to the mechanistic understanding of cell migration [14].

c-Src is a proto-oncogene tyrosine kinase. Its discovery is associated with the identification of cancer cancer-causing virus in chickens named Rous Sarcoma Virus (RSV) having the *v-Src* gene [15–17]. Later, in the 1970s, a transformed gene of *RSV* was found in normal birds, which was named c-Src. It was found that v-Src was actually a mutated form of normal c-Src captured by viruses. Later, research on its characterization and function in cells was conducted [17]. Initial research on c-Src revealed that c-Src is a non-receptor tyrosine kinase that regulates signal transduction pathways involved in cell survival, proliferation, growth, migration and apoptosis. It has also been found that mutation and overexpression of c-Src are linked with cancer [18]. This finding made c-Src a potential target for the treatment of cancer with c-Src overexpression.

FAK and c-Src play critical roles in the regulation of cell surface adhesion proteins leading to cell adhesion. The role of FAK and c-Src in cell adhesion is very crucial in various important physiological processes like, cell proliferation, apoptosis, cell differentiation and tissue formation [6,19]. Therefore, an extensive study of their interaction with other cytoplasmic proteins and subsequent activation of downstream signalling cascades is of vital importance. In this regard, the study of molecular structures, mode of activation, implication in physiological processes of cells and their link with various ailments along with therapeutic implications is considerably vital.

In this review, the detailed structure of FAK and c-Src, their mechanism of activation of FAK and c-Src, their interaction with each other and with other molecules in cell adhesion, and the role of FAK and c-Src in cell-to-ECM and cell-to-cell adhesion along with their effect on focal adhesion and adherence junctions dynamics are described. Additionally, the downstream cellular pathways triggered by FAK and c-Src and how these pathways are linked with cellular processes of adhesion, migration, and cell survival are also explained. Further, this review sheds light on the various therapeutic targets in FAK and c-Src mediated signalling to treat diseases including cancers, and how FAK and c-Src mediated signalling is related to different diseases e.g., cancer and cardiovascular diseases.

Cell Adhesion

Mechanism of Cell Adhesion

Cell adhesion is a vital process enabling cells to interact with each other or with ECM, resulting in different responses including cell proliferation, cell migration wound healing, etc. The mechanism of cell adhesion involves different types of CAMs and other cellular proteins that trigger different signalling pathways, affecting adhesion. CAMs play a crucial role in cell adhesion. CAMs are divided into four major groups, which are integrins, selectins, cadherins, and immunoglobulin superfamily [20]. These groups and their functions in cell adhesion are described below.

Cadherins

Cadherins are involved in cell-cell adhesion [21]. 20 types of classic cadherins have been reported in vertebrates [22]. They form adherence junctions by homophilic interaction of cadherin on one cell to cadherin on another cell in the presence of Ca^{2+}. Generally, classical cadherins consist of extracellular, transmembrane and cytoplasmic domains. The extracellular domain of cadherins consists of five extracellular (EC) domains, which are linked with one another via Ca^{2+} ions. The most distal extracellular domain repeat interacts with the distal repeat of the extracellular domain of cadherin on another cell in a Ca^{2+}-dependent homophilic manner. This is called trans dimerization, which leads to nascent cell-cell adhesion. Following this, clustering of the cadherin cytoplasmic domain starts. β-catenin interacts with the cytoplasmic domain of cadherin, which is strengthened by p120-catenin. β-catenin interacts with α-catenin which then binds with actin filament as shown in Fig. 1 [23].

The trans-dimer interacts with others via diffusion trapping involving cis-diffusion leading to the formation of cadherin clusters at the cell adhesion site. Cadherin clustering enlargement via the interaction of trans-dimers at the adhesion site strengthens the cell-cell adhesion via increasing strength of the interaction of cadherin with actin via catenin.

Immunoglobulin Superfamily (IgSF)

It is a diverse group of surface receptors, all of which share immunoglobulin (Ig) homology domains. Generally, immunoglobulin superfamily members consist of three main domains including extracellular, transmembrane and cytoplasmic domains. The extracellular domain consists of immunoglobin (Ig) domains, which interact with one another via disulphide linkages, and fibronectin III (FNIII) domains [24,25]. Members of the IgSF differ from one another in the numbers of Ig and FNIII domains within extracellular domains [26,27]. Immunoglobulin superfamily members regulate cell-cell and cell-ECM adhesion. Intercellular cell adhesion molecules (ICAM) and vascular cell adhesion molecules (VCAM) are members of immunoglobulin superfamily surface receptor proteins. Both regulate leukocyte adhesion to the endothelial tissues during inflammation.

The IgSF members modulate cell adhesion in the immune system as they are present on the surface of immune cells. They play an important role in the differentiation of the cells during the embryonic phase [26].

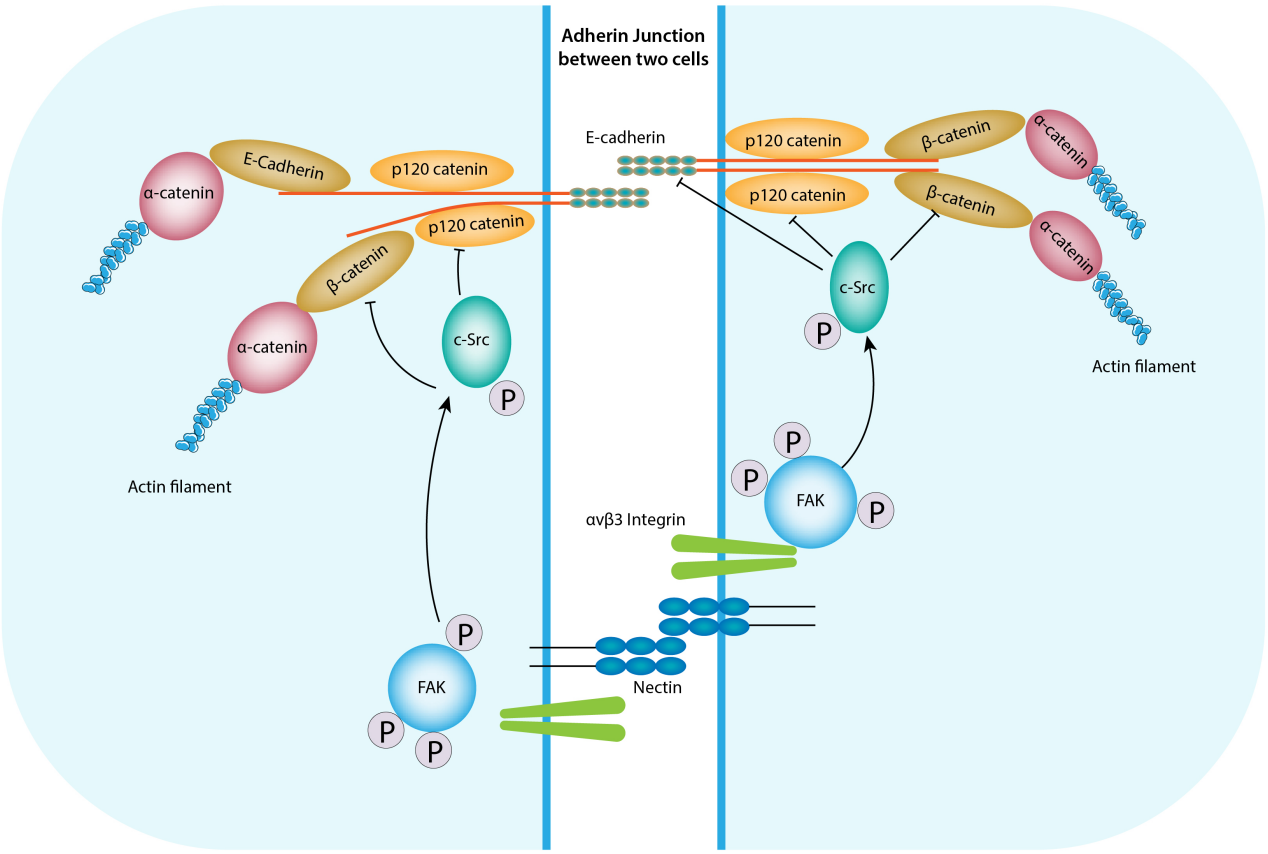

Fig. 1. Schematic illustration of FAK and c-Src in cell-to-cell adhesion sites. (Illustration is designed by Adobe Illustration 2024 Version 28.6, Adobe, SanJose, CA, USA). The FAK, c-Src, and catenin are important components of signal transduction pathways, specifically ones that are involved in cell-cell attachment sites. Both catenin and nectin are also protein families that play roles in cell-cell adhesion and signalling. Catenins are commonly associated with adhesion through cadherin, nectins play a role in forming cell junctions, especially in adherence junctions. FAK, focal adhesion kinase; c-Src, cellular-Src; p120-catenin, catenin protein with 120 kD molecular weight; E-cadherin, epithelial cadherin; P, tyrosine phosphorylation.

Selectins

Selectins are a group of cell surface receptors. They consist of extracellular, transmembrane and cytoplasmic domains. Generally, the extracellular domain of selectin consists of carbohydrate recognizing domain (CRD) or lectin domain, epidermal growth factor (EGF) like domain and consensus repeats that vary in number with the type of selectins [28]. They interact with their ligands or receptors via heterophilic interactions. The counter receptor or ligand is a highly glycosylated protein (P-selectin glycoprotein ligand-1 (PSGL-1)). The Lectin domain of selectin interacts with PSGL-1 by recognition of certain carbohydrates on PSGL-1. Hence, the lectin domain is also called carbohydrate recognizing domain (CRD). Selectins along with other carbohydrate-recognizing receptors including galectins and lectins are also present on the natural killer cell surface, which enhances the specificity recognition of carbohydrate groups on their counterpart ligand. Selectins along with integrin mediate the attachment of leukocytes to endothelium [29].

Integrins

It is the major family of cell surface adhesion receptors, consisting of heterodimer structures. In mammals, there are eight genes for α and β integrins, occurring in different combinations. In general, integrin consists of α and β subunits. Both subunits have extracellular, transmembrane and cytoplasmic domains. Together, both α and β subunits form a ligand-binding headpiece and a stalk-like tailpiece. Within the extracellular domain of α and β subunits, there are further different domains. The extracellular domain of the α subunit consists of αI, β-propeller, thigh, Calf-1 and Calf-2 domains. The extracellular domain of the β subunit consists of β1, hybrid, plexin-semaphorin-integrin (PSI), four EGF-like domains and β-tail domains [30,31]. The extracellular domain interacts with ECM components like fibronectin, collagen, and laminins. However, they also facilitate the binding of leukocytes to their counter receptor via ICAM and VCAM-1. They also mediate cadherin in cell-cell adhesion. The main role of integrin is cell attachment to the basement membrane, cell polarization and migration [32].

Structures of four classes of CAMs are summarized in Fig. 2 (Ref. [24,25,28,30,33,34]).

Role of FAK in Cell Adhesion

FAK plays a crucial role in cell adhesion [35]. It plays an integral role in the regulation of other proteins of focal adhesion like talin and paxillin, thereby modulating cell adhesion. FAK is involved in integrin-dependent signalling leading to cell motility [19], survival and proliferation; where FAK is involved in the activation of integrin and other proteins of focal adhesion [36]. FAK plays an important role in epithelial-mesenchymal transition (EMT) and cell migration during embryonic development [6,37,38]. It has been investigated that in the initial stages of adhesion, activated FAK enhances the integrin binding to ECM components like fibronectin, thereby, strengthening cell-ECM adhesion in a time-dependent manner [39].

FAK also regulates cell-cell adhesions by interacting with cadherins [40]. It has been found that in the presence of tension e.g., blebbistatin, an inhibitor of myosin-induced cell contractility, FAK directly interacts with vascular endothelial (VE)-cadherin and phosphorylates β-catenin in umbilical vein endothelial cells. Resultantly, phosphorylated β-catenin dissociates from VE-cadherin and destabilizes cell junction [41].

To sum up, FAK is involved in the modulation of cell-ECM and cell-cell adhesion by regulating integrins, cadherins and other focal adhesion proteins involved in cell adhesion.

Role of c-Src in Cell Adhesion

c-Src plays a vital role in cell adhesion. c-Src also modulates cell adhesion by interacting with integrins and phosphorylating different focal adhesion molecules including FAK, talin, paxillin and vinculin. By modulating cell adhesion, c-Src regulates cell proliferation, survival, differentiation, and migration. In cell-ECM adhesion, c-Src activates integrin by binding to their cytoplasmic tails via outside-in signalling [42].

Src also modulates cell-cell adhesion in epithelial tissue by regulating E-cadherin [43] by influencing its expression, distribution, and function in epithelial cells. Activated c-Src inhibits E-cadherin in three ways. Firstly c-Src inhibits the expression of the E-cadherin gene. Secondly, c-Src mediates internalization and endocytosis of E-cadherin by an E3 ligase called Hakai. Hakai causes phosphorylation-mediated ligation of E-cadherin molecules and induces endocytosis of ligated E-cadherin. Thirdly, c-Src also induces phosphorylation of E-cadherin and p120-catenin, causing destabilization of interaction between E-cadherin and p120-catenin. In this way, c-Src disrupts the adherence junctions by destabilizing E-cadherin interactions with p120-catenin, thus dismissing cell-cell adhesion in epithelial tissue [44].

To summarize, activated c-Src is involved in the activation of integrin and regulates other focal adhesion proteins. They also modulate cell-cell adhesion by regulating E-cadherins in epithelial cells by disrupting E-cadherin interaction with p120-catenin and disrupting adherence junctions (Fig. 1).

FAK and c-Src are highly involved in the signal transduction in cell-cell adhesion sites. In cell-cell adhesion, FAK and c-Src work together to modulate the assembly and disassembly of adhesion complexes, as well as to regulate the signalling pathways that control cytoskeletal dynamics, cell polarity, and gene expression. The interaction between FAK and c-Src is critical for the initiation and propagation of signals from cadherins and other adhesion molecules, influencing the organization of cell-cell adhesion sites.

FAK and c-Src as Key Regulators of Cell Adhesion

FAK and c-Src are non-receptor tyrosine kinases [45,46]. Both play a pivotal role in cell adhesion by regulating signal transduction pathways. FAK is activated upon signal reception by integrins from ECM [47,48]. The activated FAK recruits c-Src and activates it [49]. The activated FAK and c-Src then activate other proteins, including talin and kindlin, which start to bind with the cytoplasmic domains of integrin, thereby increasing the integrin affinity to ECM components via inside-out signalling [50]. FAK and c-Src mediated activated integrins reinforce the FAK and c-Src activation via outside-in signalling, further enhancing the clustering of cytoplasmic domains of integrins and strengthening the cell-ECM interaction and maintaining cytoskeletal organization.

Similarly, FAK and c-Src also affect the cell-cell adhesion regulating cadherins stability via phosphorylating cadherins and β-catenin. FAK and c-Src play crucial roles in cell-cell adhesion in epithelial cells. FAK and c-Src signalling is also responsible for EMT for cell migration via disruption of cadherin-mediated adherence junctions [6].

Moreover, FAK-c-Src-mediated cell adhesion plays an important role in the recycling of integrins for the dynamic availability of integrins on the cell surface by phosphorylation of proteins involved in Rab GTPase [51]. These Rab GTPases are involved in the recycling and sorting of endocytosed integrin vesicles. They are also responsible for the presentation of recycled integrins on the cell membrane [52].

Thus, FAK and c-Src get activated in response to the mechanical signals received by integrins and in turn this activated FAK and c-Src strengthen the interaction of integrin with ECM and maintain cell adhesion to ECM. The interaction of FAK and c-Src with cell surface adhesion proteins like integrins, cadherins and the consequent signalling pathways modulate cell adhesion. This modulation may cause cell migration via dynamic cell adhesion involving assembly and disassembly of focal adhesion sites on the cell membrane leading to formation and deforma-

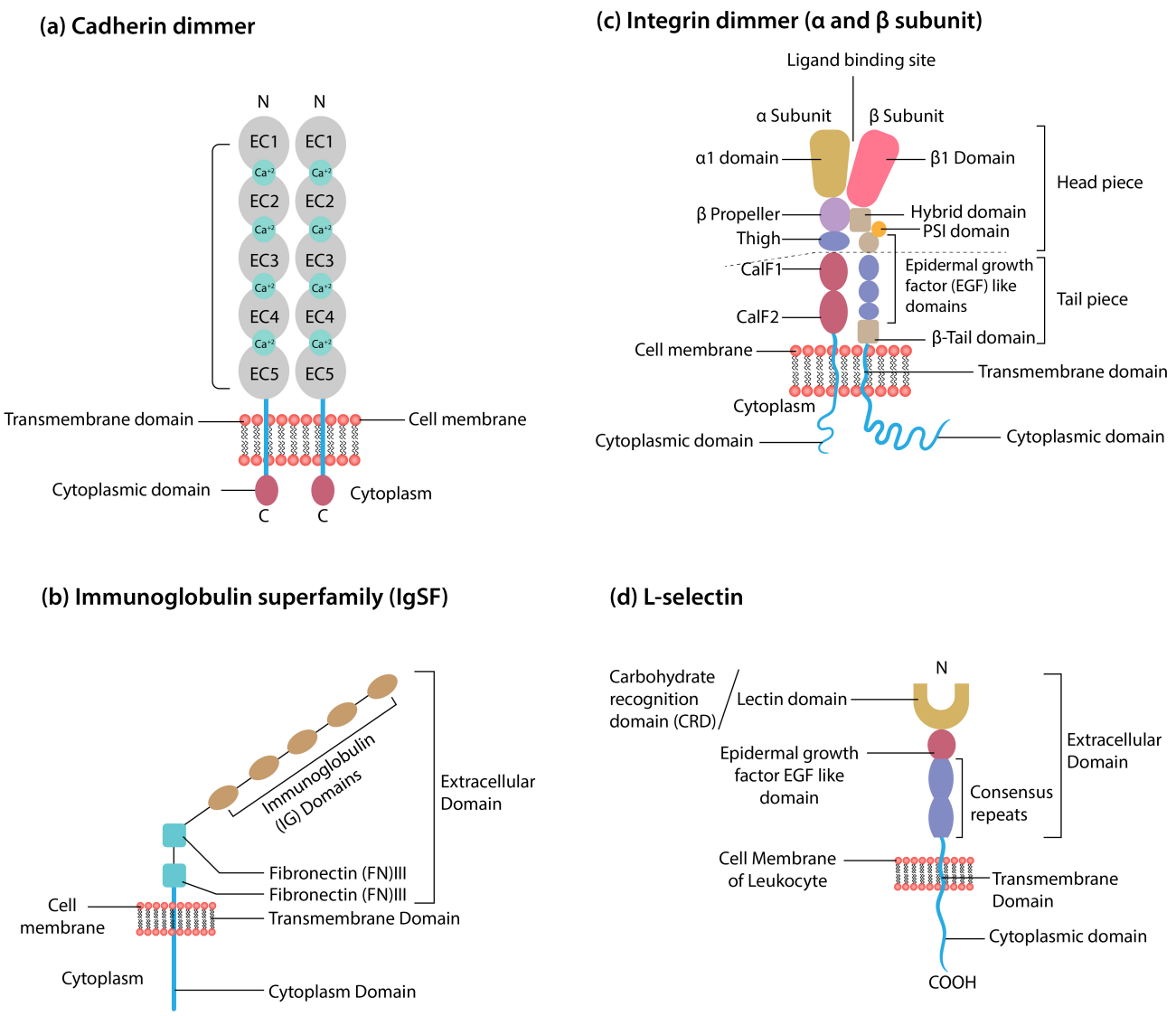

Fig. 2. Illustrations of general structures of four classes of cell adhesion molecules (CAMs). (Illustration is designed by Adobe Illustration 2024 software). (a) The general structure of a cadherin dimer with two monomers having extracellular, transmembrane and cytoplasmic domains. The extracellular domain of each monomer consists of five extracellular domains linked with one another via Ca^{2+} ions [33,34]. (b) The general structure of immunoglobulin superfamily (IgSF) with extracellular, transmembrane and cytoplasmic domains [24,25]. (c) General structure of integrin molecule with α and β subunits. Each subunit is divided into three major domains; extracellular, transmembrane and cytoplasmic domain. Extracellular domains of both subunits are further divided into a headpiece and a tailpiece consisting of different domains [30]. (d) Structure of L-selectin on leukocyte surface. L-selectin consists of extracellular, transmembrane and cytoplasmic domains. Selectins are classified on the basis of the number of consensus repeats [28]. Thigh, immunoglobulin-like domain; CalF1 and CalF2, two large β-sandwich domains; EC, extracellular; N, N-terminal domain; C, C-terminal domain.

tion of contact of cell with ECM, causing cell migration. Moreover, FAK and c-Src trigger various downstream signalling pathways involved in cell proliferation and survival. These pathways include mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) and phosphoinositide 3-kinase/Rac-α-serine/threonine protein kinase (PI3K/Akt) as described below.

FAK and c-Src-Dependent Signal Transduction in Cell Adhesion

FAK and c-Src are two important players in cell adhesion. They modulate cell adhesion by regulating integrin and other proteins involved in cell adhesion including talin, vinculin, paxillin, and α-actin. FAK and c-Src interact with each other and form a complex, which regulates many downstream signalling pathways. These pathways include

the regulation of cell adhesion, PI3K/Akt, Rho GTPase and MAPK/ERK pathways [53,54]. This section presents the details and consequences of these pathways.

Structure and Activation of FAK

FAK is a non-receptor tyrosine kinase. It has three major domains, which include N-terminal, central kinase, and C-terminal domains. The N-terminal domain is also called the erythrocyte band four-point-one, ezrin, radixin, moesin (FERM) domain. The central kinase domain is followed by 220 amino acid residues enriched with proline and has low complexity. The C-terminal domain is called the focal adhesion targeting (FAT) domain [55]. In cytosol, FAK remains in auto inhibited state by the interaction between its FERM domain and the kinase domain at certain points like Y-397 residue, thereby blocking the catalytic site of FAK. Interaction of integrin with ECM ligands induces clustering of cytoplasmic tails of integrin, which causes autophosphorylation of Y-397 amino acid residue next to the kinase domain [56]. The clustering of cytoplasmic tails of integrins also causes the binding of the FERM domain of FAK to the cytoplasmic tails of integrin, exposing Y-397 residue to be phosphorylated, thus activating FAK. The activated FAK starts interacting with SH2 domains of members of Src kinases and c-Src [55].

Epithelial cells are joined with each other via adherence junctions. There FAK is activated by integrin associated with nectin [57].

Structure and Activation of c-Src

c-Src is a non-receptor tyrosine kinase. It has an N-terminus followed by a 14-carbon myristoyl group, SH4 domain, SH3 domain, unique domain, SH2-kinase linker and protein tyrosine kinase domain and C-terminus regulatory region linked to C-terminus [58]. In an autoinhibited state, SH3 and SH2 domains interact with each other, tyrosine (Tyr)-416 residue in the kinase domain remains dephosphorylated and Tyr-527 towards the C-terminus remains phosphorylated; thereby restraining its catalytic activity [59]. It has also been reported that the clustering of integrin upon its interaction with ECM ligand induces structural changes in c-Src, which causes autophosphorylation of Tyr-418, dephosphorylation of Tyr-529 and activation of c-Src [60]. Interestingly, it has been found that G protein-coupled receptors (GPCRs) upon ligand attachment activate c-Src via its phosphorylation [61]. Growth factor receptors like epidermal growth factor receptor (EGFR) upon attaching to ligand also activate c-Src.

Cross Talk between c-Src and FAK in Signal Transduction Involving Cell Adhesion

Interestingly, FAK and c-Src cross-talk with each other. Although integrin clustering activates FAK and c-Src, they also enhance each other's activity. Thus, FAK and c-Src reciprocally regulate one another. Furthermore, both FAK and c-Src interact with each other and form a complex, which regulates several downstream signalling pathways [49].

Reciprocal Activation of FAK and c-Src

When FAK is activated by the clustering of the cytoplasmic domain of integrin, it binds with the SH2 domain of c-Src. This interaction induces conformational changes in c-Src and exposes the catalytic sites of c-Src and transforms from autoinhibited to active form enabling c-Src to regulate its downstream signalling pathways. This FAK-activated c-Src enhances the FAK activity by phosphorylating certain tyrosine residues on FAK, thereby enhancing the downstream signalling regulated by FAK [62]. In this way, both FAK and c-Src reciprocally activate each other and reinforce their downstream signalling pathways regulating cell adhesion.

Downstream Signalling by Activated FAK-Src Axis

Upon clustering of cytoplasmic tails of integrins via outside-in signalling, activated FAK-Src complexes start interacting and phosphorylating other focal adhesion proteins including talin, paxillin, integrin-linked-kinase (ILK) and vinculin. Upon FAK-Src mediated activation, these proteins directly or indirectly interact with the F-actin of the cytoskeleton of the cell, thereby enabling a connection of the cytoskeleton with integrin. Resultantly, FAK-Src-mediated activation of these protein complexes mediates different cellular processes such as cell proliferation, survival, and migration [47].

The FAK-Src-activated protein interactions lead to the activation of phosphoinositol-3-kinase (PI3K), which in turn activates Akt. Akt activates mammalian target of rapamycin complex (mTORC)1 and mTORC2. mTORC1 phosphorylates p60S6K, which stimulates the synthesis of proteins promoting cell growth, proliferation and survival including anoikic resistance. On the other hand, mTORC2 activates Ras-related C3 botulinum toxin substrate 1 (Rac), which induces cytoskeletal and focal adhesion rearrangement. Thus, FAK-Src axis plays a role in cell proliferation and survival [50].

FAK-Src complex also activates growth factor receptor-bound protein 2 (Grb2), which then interacts with son of sevenless (SOS) protein and triggers the Rat sarcoma virus (Ras)-MAPK pathway. The Grb2-mediated signalling cascade ultimately activates ERK, which in turn promotes cell proliferation, gene transcription of vascular endothelial growth factor (VEGF), promoting angiogenesis, and downregulation of E-cadherin leading to EMT [50].

FAK-Src axis also plays an important role in the activation of Rho GTPases, which promote the formation of focal adhesions and organization of actin filaments of the

cytoskeleton in the cell. Hence, by the organization of focal adhesions and cytoskeleton FAK-Src mediated activated Rho GTPase, the cell shape and motility are maintained [63].

Phospholipase C_γ (PLC_γ) is another pathway that is also regulated by the FAK axis. FAK-Src complex phosphorylates and activates PLC_γ, which consequently generates secondary messengers' diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3) from phosphoinositol bisphosphate (PIP2). IP3 and DAG stimulate Ca^{2+} release in the cytosol, which reorganizes the cytoskeleton and promotes cell growth, adhesion and motility [19].

Briefly, integrin clustering mediated activated FAK-Src complex plays a crucial role in cell adhesion. It phosphorylates different focal adhesion proteins and forms a complex, which activates an integrated complex network of signalling pathways. These activated signalling pathways promote cell adhesion, proliferation, survival, motility, differentiation, growth, and migration by rearrangement of the cytoskeleton (Fig. 3).

FAK and c-Src are also highly involved in signal transduction at focal adhesions. Focal adhesions are complex multi-protein structures that form the contact points between cells and the ECM, playing critical roles in cell adhesion, migration, and mechanotransduction. FAK is autophosphorylated at Y-397, providing a binding site for the SH2 domain of c-Src. Binding to FAK activates c-Src, which then phosphorylates FAK at additional tyrosine residues. The FAK/c-Src complex phosphorylates various focal adhesion components (e.g., paxillin, talin, and vinculin) and signalling proteins (e.g., PI3K, Grb2, and SOS), activating downstream pathways.

Importance of Cell Adhesion

Cell adhesion is essential for the cell-ECM and cell-cell communication. It regulates tissue maintenance and integrity. Interestingly, cell adhesion also regulates cell proliferation, survival, differentiation, growth, and cell migration. In normal cells, cell adhesion is tightly regulated ensuring tissue integrity and regulated cell proliferation and migration [64]. Disruption of any of the components of cell adhesion may result in serious disorders like cancers and failure of proper functioning. Regulation of cell adhesion by FAK-Src plays a very important role in embryonic development. FAK is essential for neural crest cell conversion to certain cells of the cardiovascular system. It has been reported that FAK deletion in murine neural crest cells resulted in cardiovascular malfunction [65].

Furthermore, FAK-Src plays an important role in wound healing and tissue repair in response to mechanical damage to the tissue [66]. FAK-Src receives mechanosignals from ECM and triggers the downstream pathways involved in adhesion, cell division, and differentiation [65].

Regulation of c-Src and FAK Activation and Subsequent Process of Cell Survival by their Activation

c-Src remains in an inactive state where Tyr527 is phosphorylated. There are two intramolecular interactions involving phosphorylated Tyr527, one interaction of phosphorylated Tyr527 with SH2 domain and the other is Tyr527 interaction with SH3 domain. Dephosphorylation of Tyr527 causes the release of compact conformation of c-Src to open conformation. Tyr527 dephosphorylation also induces structural changes to the SH1 kinase catalytic domain leading to autophosphorylation of Tyr416. Consequently, c-Src is converted to an active state [27]. On the other hand, binding of integrin with ligand in ECM causes autophosphorylation of Tyr397 on FAK and causes FAK activation. Integrin also mediates PIP2 to bind with the FERM domain of FAK leading to Tyr397 autophosphorylation, which also causes FAK activation. Phosphorylated Tyr397 recruits c-Src, which further phosphorylates Tyr576 and Tyr574, thereby FAK attaining a fully active state. This activated FAK activates c-Src in turn [8,51]. In this way, both c-Src and FAK regulate the activation of each other. c-Src and FAK activation cause cell survival via downstream signalling pathways [51].

In a summarized way, cell adhesion regulation by FAK-Src plays an important role in maintaining tissue integrity, embryonic development, and tissue repair (Fig. 4). Fig. 4a shows the structure of c-Src. c-Src consists of a unique homology domain 4 (SH4), an SH3 domain, an SH3-SH2 linker, an SH2 domain, an SH2 kinase linker, an SH1 kinase domain and a regulatory C-terminus. Fig. 4b shows the structure of FAK. FAK consists of three large domains (FAT, Kinase and FERM) and three proline-rich (PR) regions (PR1, PR2 and PR3) present between large domains. Fig. 4c shows regulations of c-Src and FAK activation and subsequent process cell survival by their activation.

Pathologies Arising due to Malfunctioning of FAK and c-Src in Cell Adhesion

Overexpression of FAK and Src enhances cell proliferation, survival, and migration. Uncontrolled cell division causes tumour formation while unwanted excessive cell migration results in EMT leading to metastasis, both of which are hallmarks of cancer [67].

Furthermore, FAK-Src overexpression mediates enhanced MAPK/ERK pathway activity. This results in increased levels of VEGF, promoting angiogenesis in metastatic tumours [49].

It has been reported that in smooth muscle cells of healthy blood vessels, FAK remains localized in nuclei. Vascular damage induces FAK expression. Resultantly, FAK starts to localize on the cell membrane and its activity gets enhanced. The enhanced activity of FAK in blood

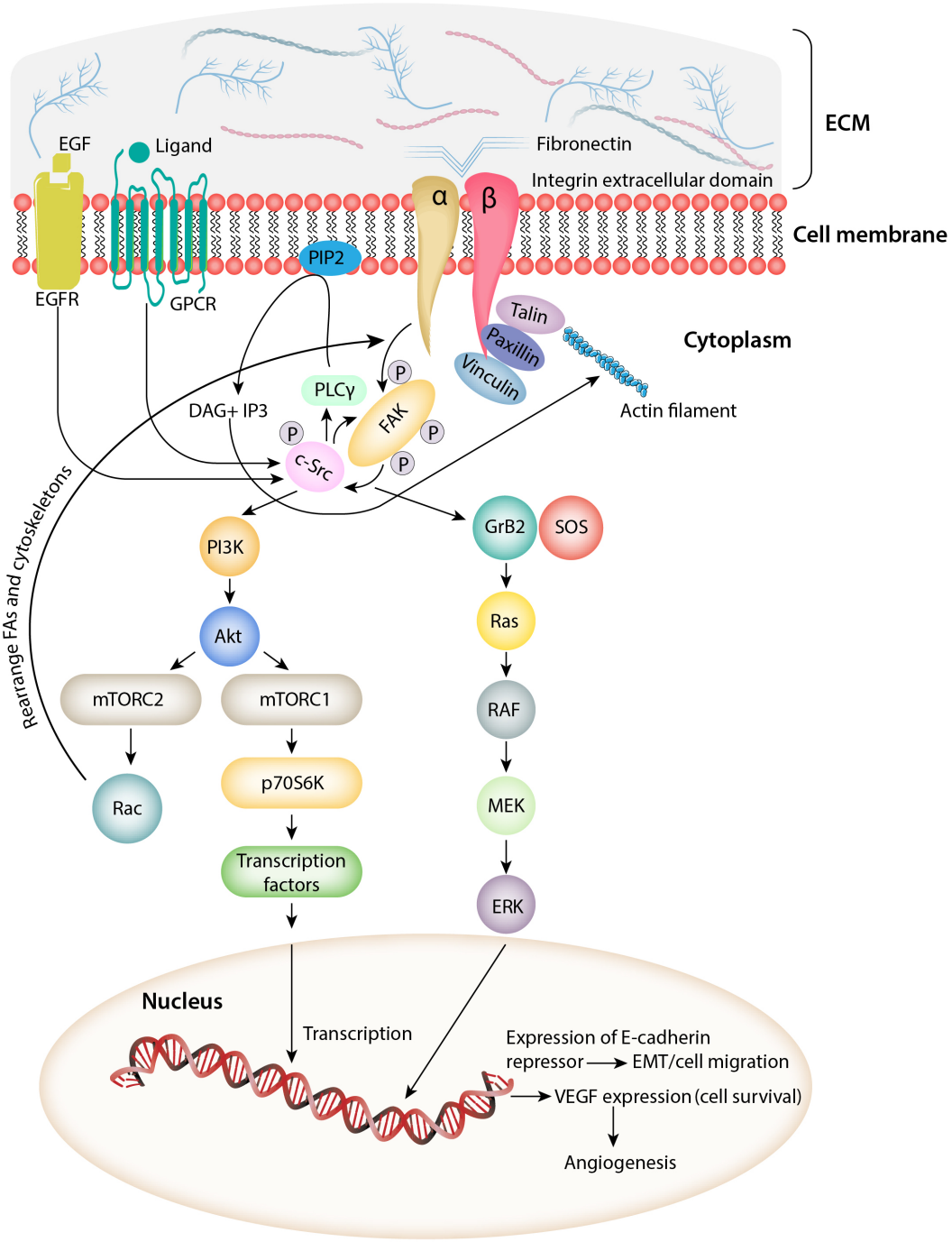

Fig. 3. Schematic illustration of FAK and c-Src in focal adhesion regulating different physiological processes. (Illustration is designed by Adobe Illustration 2024 software). The activation of the FAK-c-Src complex enables tyrosine phosphorylated residues on FAK and other focal adhesion proteins, including paxillin and which leads to the recruitment and assembly of signal transduction of focal adhesions. The actin cytoskeleton is dynamically regulated by this phosphorylation cascade, resulting in cell migration, spreading, and focal adhesion turnover. Abbreviations: EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; GPCR, G protein couple receptor; PIP2, phosphoinositol-4,5-bisphosphate; FAK, focal adhesion kinase; c-Src, cellular-Src; PLC$_\gamma$, phospholipase C$_\gamma$; DAG, diacylglycerol; IP3, inositol 1,4,5-triphosphate; PI3K, phosphoinositol 3-kinase; Akt, Rac-α-serine/threonine protein kinase; mTORC, mammalian target of rapamycin complex; Rac, Ras-related C3 botulinum toxin substrate 1; p70S6K, p70 ribosomal protein S6 kinase; GrB2, growth factor receptor-bound protein 2; SOS, son of sevenless; Ras, Rat sarcoma virus; RAF, rapidly accelerated fibrosarcoma; MEK, MAPK/ERK kinase; ERK, extracellular signal-regulated kinase; VEGF, vascular endothelial growth factor; EMT, epithelial-mesenchymal transition; ECM, extracellular matrix.

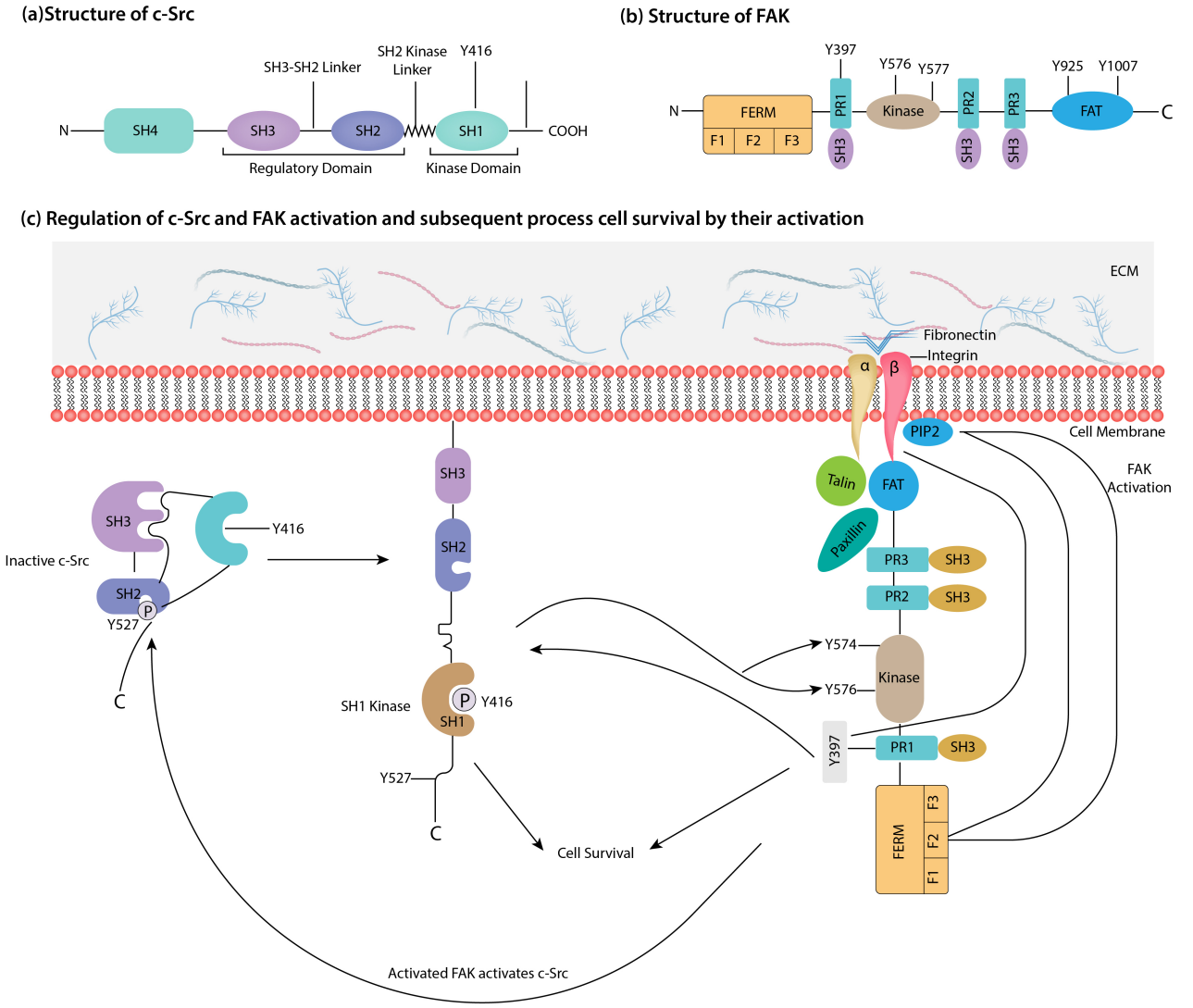

Fig. 4. Schematic illustrations of structure of c-Src (a), FAK (b), and regulation of c-Src and FAK activation (c). (Illustration is designed by Adobe Illustration 2024 software). Detailed explanation of the Figure is mentioned in section "Regulation of c-Src and FAK Activation and Subsequent Process of Cell Survival by their Activation". Abbreviations: C, C terminal domain; F, subdomains of FERM; FAT, focal adhesion kinase targeting; FERM, four-point-one, ezrin, radixin, moesin; PR, proline-rich; SH, Src homology.

vessels at the injury site enhances smooth cell proliferation, resulting in further damage by vascular smooth muscle cell hyperplasia [68]. It has also been reported that FAK modulates tumour microenvironment by creating an immunosuppressive environment [69]. Hyperactivity of c-Src induces tumorigenesis as it gets involved in oncogenic signalling [70]. The increased diversity and presentation of antigens by FAK-/- pancreatic ductal adenocarcinoma (PDAC) cells is due to Major Histocompatibility Complex class-I (MHC-I). Optimizing the pharmacokinetic properties of the peptide repertoire for high affinity binding to MHC-I requires the regulation of the immunoproteasome by FAK to determine this response [71].

Being promoters of cell survival, proliferation and immunosuppressive creators in tumour microenvironment FAK inhibitors interfere with immunotherapy against cancers. Recently, it has been clinically reported that FAK is responsible for immune evasion in ductal pancreatic cancer creating resistance to immunotherapy [71]. It has also been investigated that a long non-coding RNA LINC01089 that binds and regulates FAK activation was found down-regulated in patients with small-cell lung cancer. Consequently, FAK becomes upregulated and regulates the expression of drug-resistance genes in patients with small-cell lung cancer. This offers targeting of FAK by the introduction of LINC01089 in patients with small cell lung cancer, thereby LINC01089 serving as a FAK inhibitor [72]. Similarly, c-Src has also been reported to be linked with immunosuppression and drug resistance in ductile pancreatic adenocarcinoma. This finding supported that a combination of immunotherapy along with c-Src would be a potentially good substitute for treatment against tumorigenesis [73]. In

a recent clinical finding, levels of expression of FAK and c-Src were found to be positively correlated with stages and progression of renal cell carcinoma, suggesting the link of FAK and c-Src signalling with the disease progression. This finding provides insight into the development of an effective therapy targeting FAK and c-Src in cancer treatment [74].

To summarize, a tight regulation of FAK and c-Src is essential for normal cell functioning. Any disruption in the regulation of FAK and c-Src may result in serious pathological conditions. This makes FAK and c-Src a potential target for the treatment of cancers and other diseases associated with FAK and c-Src hyperactivity.

Therapeutic Targeting of Molecules of Cell Adhesion

Different disorders arising from a malfunction in the regulation of cell adhesions may be treated by targeting potential molecules involved in cell adhesion malfunction. The most common potentially effective targets are integrins, cadherins, c-Src and FAK. Small molecule inhibitors, antibodies and combination therapy against these target molecules may have the potential to treat different disorders arising from cell adhesion by disrupting the target [75]. Table 1 (Ref. [76–90]) exhibits inhibitors for FAK, c-Src, integrin, and cadherin along with their respective targets and mechanisms of action. Inhibitors of some of the cell adhesion proteins are presented below.

FAK Inhibitors

FAK inhibitors are used to inhibit the overexpression of FAK in cancer. They have shown considerable activity against FAK overexpression-mediated malignancies in early-stage clinical trials. One of these FAK inhibitors is VS-6063 also called defactinib, which inhibits FAK by blocking the phosphorylation of Tyr397 residue on FAK [91].

c-Src Inhibitor

c-Src also serves as a target in cancer therapy and diseases linked with c-Src overexpression [92]. Dasatinib is reported to inhibit c-Src activation and minimise cell migration in the human non-small cell lung cancer (NSCLC) cell line [93].

Integrin Inhibitor

Integrin inhibition has also the potential to treat cancer, metastasis and chronic inflammation [94]. Several drugs which act as integrin inhibitors have been utilized and many are currently being tested via preclinical trials. One of the approved drugs is efalizumab, which inhibits lymphocyte binding $\alpha L\beta 2$, thereby inhibiting lymphocyte activation and migration [95].

Cadherin Inhibitors

Cadherin is involved in cell-cell adhesion. It has the potential to serve as a target for cancer treatment [96]. Such monoclonal antibody called BV14 has been synthesized that can bind to the EC4 region of V and E-cadherins, thereby inhibiting metastasis, cell proliferation and angiogenesis. In this way, it stops the progression of lung cancer glioma [76].

Future Perspectives and Challenges

FAK and c-Src are two important proteins as they define the fate of cell adhesion by regulating other cell adhesion proteins. Their expression is tightly regulated; thus, any disturbance in their expression may result in different disorders like cancer, glioma, cardiovascular diseases and altered development. Many inhibitors of FAK, c-Src and other cell adhesion proteins have been developed to treat disorders arising from their malfunction. Cell adhesion may offer further potential targets, particularly those involved in FAK-Src signalling, in the development of therapy against these diseases in the future.

However, there are different factors that are challenging to develop the therapy by targeting cell adhesion molecules. Some of these may include resistance to the drug developed against the target [70]. Cytotoxicity is another factor that is challenging to this therapeutic strategy [97]. As a result, more research in this area is required, as is the development of novel drug development techniques. A further development of potent inhibitors of different adhesion signalling targets is required.

Discussion

This review points out the pivotal roles of FAK and c-Src in regulating cell adhesion. Cell adhesion is a critical phenomenon responsible for regulating other cellular processes including cell survival, proliferation, tissue formation and motility. The process of cell adhesion involves different proteins leading to the formation of focal adhesion sites. These proteins include CAMs on the surfaces of different cells and other cytoplasmic proteins including FAK, c-Src, paxillin, tallin and vinculin, etc [98,99]. CAMs include four major classes including cadherin, integrin, IgSF and selectins [100]. FAK and c-Src are two non-receptor tyrosine kinases, which exist in an inactive state in the cytoplasm via autoinhibition. FAK-Src axis is a vital regulator of cell adhesion leading to different cellular processes. Interestingly, FAK and c-Src cross-talk with each other and reciprocally activate each other [49]. FAK and c-Src are activated by the interaction of integrin with ECM and in turn, different signalling pathways are triggered including ERK/MAPK and PI3/AKT pathways, which promote cell survival and cell proliferation [53,54].

Table 1. List of inhibitors (FAK, c-Src, integrins and cadherins) along with their respective targets and mechanisms of action.

Drug (Inhibitor)	Target	Mechanism of action	Type of the disease	Reference
PF-562271	FAK	Inhibits kinase activity of FAK	Cancers, solid tumours	[77]
VS-4718	FAK	FAK inhibition, thereby blocking the tumour cell proliferation and survival and metastasis	Cancers	[78]
Defactinib	FAK	FAK signalling inhibition leads to tumour growth and metastasis reduction	Cancers, solid tumours	[79]
VS-6063	FAK	FAK inhibition and reducing tumour cell survival	Ovarian cancer	[80]
Dasatinib	Src	Inhibits kinase activity of the Src family of kinases, thereby inhibiting tumour cell proliferation, survival and metastasis	Solid tumours	[81]
Bosutinib	Src	Src kinase and Abl kinase activity inhibition, thereby inhibiting tumour cell proliferation and growth	Chronic myeloid leukaemia	[82]
PP2	Src	Inhibition of the Src family of kinases, reducing tumour growth and metastasis	Cervical cancer	[83]
E7820	$\alpha5\beta1$ integrin	Downregulates the expression of integrin, thereby inhibiting angiogenesis	Colorectal cancer, renal carcinoma	[84]
Cilengitide	$\alpha V\beta3$ and $\alpha V\beta5$ integrin	Inhibit angiogenesis and metastasis	Glioblastoma	[85]
Tirofiban	$\alpha IIb\beta3$ integrin	Inhibition of platelet aggregation via fibrinogen binding blockage	Cardiovascular disorders, Acute coronary syndrome	[86]
Lifitegrast	LFA-1 integrin	Inhibition of T-cell adhesion and migration	Dry eye disease	[87]
Vedolizumab	$\alpha4\beta7$ integrin	Inhibition of T-lymphocyte trafficking to the gut	Inflammatory Bowel Disease (IBD)	[88]
RGD peptides	Integrins	Inhibition of integrin-regulated cell adhesion	Cancers, cardiovascular disorders	[89]
Exherin (ADH-1)	N-cadherin	Inhibits the interactions of N-cadherin with different molecules in cell adhesion signalling and induces apoptosis	Solid tumours	[90]
BV14	VE-cadherin	Bind to the EC4 region of V and E-cadherins, thereby inhibiting metastasis, cell proliferation and angiogenesis	Lung cancer glioma	[76]

Abbreviations: N-cadherin, Neural cadherin; VE, vascular endothelial.

Although cell adhesion regulates cell survival and proliferation, overexpression of different molecules involved in cell adhesion may result in various pathological conditions including different types of cancers cardiovascular diseases, eye diseases, and autoimmune disorders like ulcerative colitis and Crohn's disease. FAK and c-Src activation triggers different signalling cascades that promote cell survival, proliferation and migration. Therefore, the overexpression of FAK and c-Src results in major hallmarks of cancer including; uncontrolled cell proliferation, inhibition of apoptosis and enhanced cell migration (epithelial to mesenchymal transformation EMT) [49,67]. Therefore, tight regulation of FAK and c-Src expression is mandatory for normal cell functioning.

Being linked with different types of diseases, FAK and c-Src have the potential to be targeted for the treatment of those diseases linked with FAK and c-Src overexpression. In this regard, many small molecule inhibitors of FAK and c-Src, which are under preclinical and clinical trials, have been introduced to treat subsequent disorders. Many drugs against FAK and Src have already been introduced in the market including dasatinib and bosutinib [101]. Similarly, inhibitors of integrin and cadherin also have been introduced which inhibit FAK and c-Src activation and their subsequent events leading to the malfunctioning of cells. Further drugs and inhibitors may be developed in the future against different targets involved in cell adhesion and its subsequent cell signalling pathways to treat different diseases linked with cell adhesion malfunctioning.

Despite of introduction of different therapies involving small molecule inhibitors against different molecules in cell adhesion like FAK and c-Src, there are still many factors that are challenging for these targeted drug therapies. These factors include drug resistance and cytotoxicity. Furthermore, the side effects of drugs associated with drug treatment are another difficult issue that must be addressed. Likewise, dasatinib treatment is associated with the side effects of pulmonary hypertension and pleural effusion. In this regard, it is needed to address these side effects associated with dasatinib administration [102]. The development of combination therapy and the use of reduced drug doses might be a good substitute to resolve the drug treatment-

associated side effects. For this purpose, it is necessary to have deep research into the mechanisms linked with the drug-associated side effects. This is a significant gap in the literature. For this purpose, further *in vivo* preclinical and clinical research is required. This would help trace out the potent target for the development of combination therapy to minimize the drug-associated side effects. The introduction of novel techniques in drug development and further potent inhibitors against different cell adhesion signalling targets is needed. Thus, drug resistance and drug-associated toxicity are major challenges to drug development against cell adhesion targets, which may lead to innovation in future research.

To close, there is a need to explore the FAK and c-Src in further diseases like fibrosis where cell adhesion and migration have integral roles in disease occurrence. The invention of more effective and specific inhibitors with more efficacy and safety needs to be focussed on in future research.

Conclusion

In conclusion, cell adhesion is a critical biological marvel, which is linked with different developmental processes including cell proliferation, differentiation, and tissue formation. FAK and c-Src are two cell adhesion proteins, which play a critical role in cell adhesion. They modulate cell adhesion by serving as regulators of different cell adhesion proteins. Any disturbance in their expression or their over-expression may cause pathological conditions such as cancer, cardiovascular disorders, and developmental anomalies. Thus, being an integral part of cell adhesion, different proteins in FAK-Src signalling may be targeted for drug development in treating these disorders. Hence, the research into FAK and c-Src signalling is a promising field, which has potential in certain novel therapeutic approaches against various diseases arising from altered signalling pathways involved in cell adhesion.

Availability of Data and Materials

Not applicable.

Author Contributions

The author (KK) made substantial contributions to conception and design, or acquisition of data, or analysis and interpretation of data. The author drafted the manuscript and revised it critically for important intellectual content. The author gave final approval of the version to be published. The author participated sufficiently in the work to take public responsibility for appropriate portions of the content. The author agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The author declares no conflict of interest.

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