Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 9[4] March 2020 : 138-143

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD
Global Impact Factor 0.876
Universal Impact Factor 0.9804
NAAS Rating 4.95

REVIEW ARTICLE **OPEN ACCESS**

Actin-Bundling Proteins in Cancer Progression: A Review

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ABSTRACT
Cancer cell metastasis is a multi-stage process involving invasion into surrounding tissue, intra-vasation, transit in the blood or lymph, extra-vasation, and growth at a new site. Many of these steps require cell motility, which is driven by cycles of actin polymerization, cell adhesion and acto-myosin contraction. These processes have been studied in cancer cells in vitro for many years, often with seemingly contradictory results. The challenge now is to understand how the multitude of in vitro observations relates to the movement of cancer cells in living tumor tissue. The actin cytoskeleton plays crucial roles in trafficking and signaling at both the cell cortex and organelle periphery but the exact contribution of actin bundles remains unclear. This review gives an outline of the role of actin-bundling in cellular structures and discusses how alterations in the activity or expression patterns of actin-bundling proteins could be linked to cancer initiation or progression.
Keywords: *Actin, Fascin, Microvillus, Invodopodium, Metastasis, and Cancer*

Received 27.01.2020 Revised 11.02.2020 Accepted 15.03.2020

INTRODUCTION

Cells are utilizing their cytoskeletons to move, polarize, isolate and maintain association inside multi-cellular tissues. Actin is an exceedingly moderated fundamental building block of the cytoskeleton that structures links and struts, which are continually redesigned by in excess of 100 different actin-bundiling proteins.

The initiation of new actin filaments and their consequent organization is a key step in the development of specific cell structures, for example, filopodia, microvilli, and invadopodia. While the cytoskeleton is important in normal cellular function, it can be subverted in cancer cells and contributes to changes in cell growth, stiffness, development and invasiveness.

Actin is one of the most abundant proteinsin mammalian cells, and underpins the compartmentalization of cell substances and motility. Filaments are assembled into superstructures by actin-filament-bundling proteins. Some bundling proteins (e.g. fascin and a-actinin) form parallel bundles, while others (e.g. filamin) form looser orthogonal meshwork. In general, cross linking proteins have two actin-bundiling sites, often because they dimerise, and the location of actin-bundiling sites determines the filament arrangement and type of crosslinked structure formed.

Actin filaments are polar, with a fast-growing and a moderate developing end, and this polarity is maintained by a cycle of ATP hydrolysis. Bundling proteins can be particular about the introduction with which they bind tothe filament, permitting the specific formation of bundles of either mixed or uniformpolarity. Bundling proteins areoften modular and contain repeated actin filament-bundiling areas. For example, the calponin-homology domain(CH domain), gelsolin domain and spectrindomain are used by many actin bundlers.

ACTIN-BUNDLING PROTEINS IN CANCER METASTASIS

Metastatic tumor cells utilize actin groups to support distensions that permit them to split a long way from essential cancer and attack through the encompassing tissue. In the wake of going into the vasculature or lymphatic systems, they exit into another specialty and seed another malignancy, regularly in the wake of lying dormant for a considerable length of time or years. Amid metastasis, cells adjust their motility and adhesive ability to suit their condition[1 & 2].

ACTIN-BUNDLE IN NORMAL AND CANCER CELLS

Non-muscle myosin IIα and IIβ are the primary actin-based contractile myosin motors that cross-connected with actin fibers of cell cortex and regulate cell solidness. Phosphorylation of the light chain myosin II triggers the contractile action of myosin II[3]. Abnormal amounts of the myosin kinase Rho-associated protein kinase 1 (ROCK1) are engaged with poor survival of patients with breast cancer[4] and connect with poor tumor separation, muscle invasion and lymph node metastasis in bladder cancer[5]. The consequence of a clinical report demonstrated a positive relationship between myosin light chain kinase, with illness repeat and metastasis in non-small cell lung malignancy[6]. The best reagent for the identification of dynamic myosin II or particular enhancement of myosin II isoforms is required for advance conformation[7]. Growths can also impact the contractile properties of stromal cells, for example, fibroblasts[8-10]. Expanded stromal cell contractility advances matrix stiffness, which leads to tumor-promoting properties[11] by upgrading integrin connection, signaling, activation pro-survival and development signals, for example, actuation of focal adhesion kinase (FAK)[12]. Though, myosin II forms parallel contractile group filamin proteins, pivoted actin bundlers that give mechanical strength and signaling frameworks near membranes. Filamins are mechanosensors, which control translation, membrane trafficking, particle channel function, adhesion and receptor-mediated signaling [13]. Filamin ties to the androgen receptor by framing a complex with β1 integrin and adjusts cell-motility reactions downstream of androgen signaling, which could drive attack in the prostate tumor[14 & 15]. Filamins likewise shape a complex with pro-prion protein (PrP) in pancreatic malignancy. A similar complex may contribute the progression of melanoma[16]. Filamin adjusts hepatocyte growth factor receptor (HGFR), otherwise called the proto-oncogene Met signaling, which is significant for the metastasis of numerous epithelial malignancies to metastasize[17]. Filamins may likewise shape a piece of the molecular skeleton, where they interface with DNA repair complexes, for example, breast cancer type 1 susceptibility protein (BRCA1)[18] and with cell cycle movement proteins, for example, cyclin D1 (CCND1)[19]. An emitted variation of filamin has been recognized in the blood of patients with cutting-edge metastatic breast cancer and astrocytomas, demonstrating that filamin may have a prognostic esteem [20].

Spectrins, otherwise called Fodrins are another class of key actin cross-linkers of the cell cortex, which have been involved in cancer. In colorectal and pancreatic malignancies, β2-spectrin ties and manages the progression of transcriptional activators, in particular, SMAD3 and SMAD4 of the transforming growth factor β (TGFβ) signaling pathway. TGFβ signaling typically goes about as a malignancy suppressor of the colorectal tumor by suppressing development and advancing apoptosis, however, its dysregulation through loss of β2-spectrin improperly initiates Wnt signaling and advances cancerogenesis [21]. Embryonic spectrin likewise called as embryonic liver fodrin indicated modified expression in specific kinds of tumors and its misfortune causes deregulation of cyclin D1 and abnormal cell cycle progression[22]. α Actinin-1 and 4 localized at cell-cell contacts[23] where they direct actin bundling and epithelial integrity. α-Actinin-4 binds to and enlists the tight intersection protein known as junctional Rab13 bundiling protein (JRAB) and molecule interacting with CAS-like 2 (MICAL-L2). Along these lines takes part in tight intersection development. Tight intersections lie apical to adherents intersections and keep up impermeability of epithelial tissues. Loss of α-actinin-4 disturbs the integrity of tight intersection and has been related to malignancy invasion and additionally metastasis[24]. Be that as it may, in many examinations, abnormal amounts of α actinin-4 relate with poor outcome[25-35], and the significance of its part in tight intersection gathering for cancer thus remains unclear. Different elements of α actinin-4 are the association in the main edge distension[25] that may add to metastasis and further examination is justified.

Microvillus

Microvilli are finger-like projections of the plasma membrane that proliferate the surface area of cells to improve the retention and emission. Intestinal brush-border microvilli contain a parallel actin bundle center made up of around 40 actin fibers of uniform extremity are cross-connected by no less than three distinctive actin-bundling proteins, for example, T-plastin or T-fimbrin, villin and small espin[36 & 37]. Microvilli likewise contain the cortical parts like spectrin and myosin II in the terminal web is otherwise called actin meshwork at their base [38] and is bound to the apical surface by brush border myosin I. T-plastin is a monomeric protein, profoundly expressed in the small digestive system, which crosslinks F-actin into straight packages[38 &39]. L-plastin is likewise called as L-fimbrin is regularly just present in hematopoietic cells; in any case, an investigation demonstrated that it is communicated in most of the epithelial cancers and non-epithelial mesenchymal cancer [39]. The expression of L-plastin additionally connects with stage and seriousness of colorectal malignancy. It is considered as a potential prognostic pointer for colorectal tumor [40& 41]. Villin mediates bundling, the start of new fibers (nucleation), capping and disjoining of actin fibers in a Ca2+ subordinate way [42], and is exceedingly expressed in

adenocancers beginning from epithelial cells of the intestinal tract that bear brush outskirt microvilli [43 - 45]. Small espin adds to an extension of microvilli from the barbed end of the actin bundle, however, has not yet been ensnared in malignancy. In harmful cells, an expanded number of microvilli with unpredictable morphology can be associated with metastatic status [46& 47], however, its centrality is hazy.

Filopodium

Filopodia are the long, thin, actin-based projections that advance cell movement and add to tumor cell attack[48&49]. The parallel actin-bundling protein fascin is found in filopodia, however, is regularly communicated in cells got from mesenchymal and neural sources instead of epithelia [50-52]. Expression of Fascin is regularly up-controlled in epithelial cancers and related to invasion and in addition cancer metastasis [53]. Fascin-mediated actin bundle formation strengthness fibers and increment the lifetime of both filopodia and obtrusive projections [16]. Fascin is profoundly communicated at the invasive front of tumors, and *in vitro* decrease of fascin causes diminished motility and invasion [54-56]. Formins are additionally filopodial proteins with both actin-nucleating and actin-bundling action. The actin-bundling FH2 areas of mDia1, mDia2 and in addition mDia3 dimer formation [57]. Very little is thought about the part/s of the Dia proteins or to be sure the other 12 mammalian formins in malignancy. The Ena/VASP proteins (VASP and Evl invertebrates) contain a group of proteins that advance actin polymerization and packaging and connect with filopodia tips, and additionally with lamellipodia, cadherin-based cell-cell contacts [58-60] and focal adhesions [61]. As of late, a splice variant of Mena, named as Mena INV, was observed to be over-expressed in breast and colorectal malignancies [62]. Mena insufficiency diminishes invasion, metastasis and tumor progression in polyoma middle-T transgenic mouse models and disables ordinary breast development [63-64].

Invadopodium

Invadopodia are dynamic actin-rich membrane bulges discovered just in invasive cancer cells. They contain a blend of bundled and extended actin [56] and are utilized for matrix redesigning. Podosomes are basically and practically like invadopodia but happen in hematopoietic cells, endothelial cells and Src-transformed fibroblasts [65]. Invadopodia and podosomes contain various actin packaging proteins, including fascin [54&56], α actin in, formins and Ena/VASP proteins [65].

CONCLUSION

Cancer metastasis represents the most destructive part of most cancers and also perhaps one of the most exciting frontiers for modern biomedical examination.The actin cytoskeleton represents a major network of proteins that encroach on motility, invasion, polarity, survival and growth of normal cells, and all things considered is regularly subverted by tumour cells. Over-expression of facin is linked to increased aggressiveness in a number of cancer types, including breast and colon carcinoma. Therefore, fascin is increasingly cited as both a potential biomarker and therapeutic target in many types of cancer.This review demonstrates how tumours manipulate the cytoskeleton to gain advantage and to reveal those key proteins that may be future targets against invasion and metastasis.

ACKNOWLEDGMENT

We are thankful to Professor and Head, Department of Pharmacy for providing sufficient research facilities.

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CITATION OF THIS ARTICLE

A.Vijay, K. Kathiresan, P. Pandian Actin-Bundling Proteins in Cancer Progression: A Review. Bull. Env. Pharmacol. Life Sci., Vol 9[4] March 2020 : 138-143