



Expression of Cytoskeleton Actin in Cancer and Metastasis

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Abstract

Cytoskeleton in Eukaryotic cell is very important for cell to keep the exact shape and supports the plasma membrane and give the mechanical support to cell. Actin is a type of cytoskeleton that is involved in several functions. Actin filaments are made up of indistinguishable actin binding proteins which is set in a lengthy curved chain which performs important function of body. Expression of some actin binding proteins are regulated during carcinogenesis and metastasis, these proteins include Arp2/3 (Actin related protein 2 and 3 complex), fascin and the tropomyosin's, WASP/WAVE (Wiskott-Aldrich syndrome protein/WASP and Verprolin homologous protein) complexes. The expansion of cancer cells from the primary tumor to other tissues and the organs is called metastasis. The connection amongst the hyperactivated signaling pathways plays a very important role in the development of metastatic. GPCRs (G Protein Coupled Receptors) through β -arrs (β -arrestins) act as a intracellular signaling particles. In tumor cells the increased and decreased expression of these actin binding proteins are involved in progression of different types of cancer and metastasis.

For further insight we have to understand what is actin and the function of actin binding proteins.

Keywords: Cytoskeleton, Actin, Cancer, Metastasis

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INTRODUCTION

Cytoskeleton in Eukaryotic cell is very significant for the cell to keep the overall shape and give the mechanical support to cell to perform different functions like movement, division and make available the pathways for vehicles to transport (1).The cytoskeleton is made up of different filamentous protein basically it is divided into 3 major classes which have different sizes and composition of protein. The 3 classes include microtubules which is the largest type filament with a diameter of 25 nm, it is used for the transportation within the cell and the next is intermediate filaments made up of fibrous proteins and have a diameter of 8-10 nm and it performs the basic function which is forming a network that grips the different organelles and nucleus in one place, and it resides in between the microtubules and microfilaments, which is the third filament protein and the smallest one with the diameter of 6nm and made up of a protein called actin which is double helix and are made up of actin monomer (2).The Actin protein is very important in the motility of muscle cells and other cells. It exists in two guises one is G-actin and the other is F-actin, they are also called monomeric globular actin and polymeric fibrous actin, respectively. The f-actin form is involved in muscle tightening.

Actin Filaments

Actin filaments are made up of indistinguishable actin proteins which is set in a lengthy curved chain ("Microtubules

and Filaments," 2014). It was first discovered in skeletal muscle. Basically, actin filament like every other protein perform some specific functions in our body. It helps a motor protein called myosin as a pathway for movement. For example, a ring made up of actin and myosin tweak the cell away from each other so they can produce two new daughter cells in animal cell division. The most important property of actin filament is they can congregate and disassemble very fast which consent them to perform significant role in cell motility like dragging the white blood cells in the immune system (3). There are some actin binding proteins whose expression is regulated throuout the time of carcinogenesis and metastasis.

Cancer and Metastasis

There are many conditions like radiation, mutations, viral infections etc. through which normal cells initiate into abnormal cells and start to divide and spread into other tissues without stopping, is called cancer. The expansion of cancer cells from the prime tumor to further tissues and the organs is called metastasis and is the prime cause of cancer disease and death caused by cancer. 90% of cancer death is caused by metastasis (4). There are multiple consecutive events known as metastatic cascade which have to be completed to efficaciously metastasize the tumor cells, and this metastatic cascade is divided into three processes the first is invasion the second is intravasation and the third one is extravasation (5).The method of invasion is the loss of cell to cell attachment and it will permit



the tumor cells to detach them from the prime tumor form and changes in cell matrix contact which allow the cells to conquer into the other stroma. Intravasation course involves the excretion of elements to deteriorate the basement membrane and extracellular matrix. The expression and destruction of proteins to control the movement is also involved in intravasation. The process called angiogenesis must be determine by tumor cells to develop further. The process of extravasation is the association between the tumor cell and other stroma. It is tremendously significant in the expansion of tumor angiogenesis. After reaching the expected point, the tumor cells conjoin with the endothelial cells by enduring biochemical interaction which develop the bond through the endothelial cells to form a stronger connection and therefore they can enter into the basement membrane and endothelium cells (6).

GPCRs Through B-Arrestins (B-arrrs)

The connection amongst the hyperactivated signaling pathways plays a very significant role in the growth of metastasis. G-protein (actin) coupled receptors (GPCRs) is extremely important in the progression and metastasis of cancer (7). The operating and signaling of many GPCRs is regulated by a family of adapter protein called β -arrestins, consisting of β -arrestin1 and β -arrestin2. It is involved in the modulation of cell propagation, endorses the cell invasion and movement of cell, the progress percentage of tumor, angiogenesis, drug resistance and spread anti apoptotic persistence signals etc. It plays significant role in cancer progression during hyperactivated signaling pathways. GPCRs through β -arrestins (β -arrrs) acts as intracellular signaling particles so they can integrate into other pathways to regulate the metastatic process (8).

Actin Binding Proteins

As discussed, earlier there are some actin binding proteins whose expression is regulated during carcinogenesis, these proteins include Arp2/3 which is known as Actin related protein 2 and 3 complex, fascin and the tropomyosin's, WASP/WAVE which is known as Wiskott-Aldrich syndrome protein/WASP and Verprolin homologous protein complexes. These all proteins expression are involved in the regulation of carcinogenesis.

Arp2/3

The Arp2/3 is an evolutionary preserved mechanism whose proteins play an important role in functioning of actin. The Arp2/3 complex makes the branched actin network. According to the latest findings the over activation of the Arp2/3 complex promotes the development of cancer(9). Found by immunohistochemistry the subunits of Arp2/3 mostly overexpressed in different types of cancer like breast cancer, gliomas, colorectal cancers, lung and gastric cancers. When analyzed through PCR the Arp2, ARPC2 and ARPC3 are found to be reduced in cancer samples. Poor prognosis for patients is usually associated with the overexpression of Arp2/3 (10).

WASP and WAVE Family

To change the shape, division and movement, the cells need to rearrange their actin cytoskeleton. The Wiskott-Aldrich syndrome protein (WASP) and WASP-family verprolin-homologous protein (WAVE) family proteins are the abundant restructures of actin cytoskeleton found in all eukaryotes. Their key function is to take upstream indications from Rho-family small GTPases and activate the Arp2/3 complex through which the actin polymerization occurs rapidly, critical for some cellular developments like endocytosis and cell motility (11). WASP/WAVE are not only important for healthy cells but also perform role in many types of cancer. Latest research proved

that WASP/WAVE proteins are related with the migratory, metastatic and invasive actions of different types of cells (12).

Tropomyosin as Regulator of Cancer Cell

The most studied and researched structural proteins of the cytoskeleton are tropomyosin. It plays significant part in actin organization and the anchorage dependent progression of cells, also classified as tumor suppressor(13). Their is decreased expression of tropomyosin related with the tumors that metastasize and invade in bladder, breast, prostate and colon cancer. If there is mutation in tropomyosin than it will cause the growth and progression of cancer cells. It is overexpressed in many cancers when compare with normal cells. The over expression stabilize the F-actin and rise the quantity of cell to cell connection which decreases the migrant potential of endothelial cells (14).

Hippo-YAP

YAP (Yes-associated protein) is present in the cytoplasm. It is an oncoprotein. Oncoproteins are proteins which play a significant role in the synthesis of those proteins which are associated with tumorigenic cell development. Some of them are used as tumor markers. It is in non-functioning inactive state but when it activated it travel to the nucleus and triggers the transcription of those genes who are accountable for cell division, invasion, migration and apoptosis. YAP is present in Hippo Signaling pathway (which controls the size of organ in animal) and it is a regulatory protein which perform important functions such as cell regeneration and propagation (15). In recent studies shows that YAP perform several other important functions apart from regeneration and propagation. For instance, we found that YAP advanced contractile actin structure formation by up-regulating nonmuscle myosin light chain articulation and the generation of cellular ATP (16). The migration of carcinogenic cell into blood vessels or lymph nodes leading to metastases is important for the development of cancer. For the propagation of tumor, the cancerous cell can move as single cell or collectively in a group in a lamellipodium based migration mode (17). Cellular membrane under this condition, expand in lamellipodia and it is determined mainly through F-actin polymerization. Cofilin is one of the indispensable controller Actin binding protein which is the main regulator of F-actin polymerization and also regulate the formation of lamellipodium (cytoskeletal protein) (18). In the recent studies it is shown that YAP pathway is the upstream regulator of cofilin/F-actin and for the progression of HCC (Hepatocellular carcinoma) the Hippo YAP plays an important role. In HCC the deletion of YAP resulted in the migration inhibition. The expression of YAP which was momentarily upregulated in HCC, helped the cell movement. YAP expression was increased in tumor cells tissues compare to usual liver tissues, also YAP has the capability to effect cellular invasion and cell movement. The loss of YAP reduced the quantities of moved and invaded cells when contrasted with the control group. Altogether, these outcomes distinguishes Hippo- YAP as tumor agent in primary liver cancer that is facilitated via stimulation of cofilin/F-actin/lamellipodium (19).

ECM and FASCIN-1 Expression in Cancer

The Extracellular Matrix (ECM) is defined as a three-dimensional system of additional cellular macroparticles e.g. enzymes, collagen and glycoprotein. In surrounding cells they offer the mechanical and biochemical support (20). There are number of dynamic cellular progressions like variation, expansion, cell persistence and tissue hemostasis in which ECM and their interaction with actin cytoskeleton are important and this phenomenon is mainly for parenchymal liver cells called

hepatocytes. These cells greatly interact with ECM and shows a numbers of focal adhesion and actin associated proteins (21).

Carcinogenesis in liver is very common and ECM plays a significant role to develop HCC because those cell adhesion proteins which connect hepatocytes cells to the ECM are found to play significant role in the progression or development of HCC, and those cell adhesion proteins are mostly associated with actin protein either in direct or indirect way (11). Cell attachment to single macro-molecules of the extracellular matrix has dramatic possessions on the sub-cellular localization of the actin-bundling protein fascin-1 and on the capability of cells to form constant fascin-1 micro spears (22).

Fascin-1 is found in membrane ruffles and stress cells. Fascin-1 is not manifested in normal epithelial cells, however it is overexpressed in the inflammatory infiltration and neoplastic cells. Fascin-1 binds with β -catenin, pertains to a Wnt signaling pathway and is liable for cellular adhesions. Wnt is a group of proteins having a requisite role in carcinogenesis. Overexpression of Fascin-1 forms filopodia. These are structures accountable for migration of cells, their invasiveness and increase propagation of neoplastic cells (23). In transformed cells the expression of fascin-1 is shown to be increased, especially in HCC this protein has been associated with the development of deprived prognosis for HCC patients. Fascin-1 is extremely upregulated in HepG2 cell line of HCC and further the cell adhesion cells in HepG2 cells shows that Fascin-1 reduction stabilizes cells of ECM adhesions. As we already discussed that ECM and actin cytoskeleton is important for the development of HCC and in ECM there is a protein present called magflin which is a focal adhesion protein (also known as Filamin Binding LIM-protein-1) and VASP which is also a focal adhesion protein and do the regulation of actin polymerization and fascin-1 is regulate the magflin and VASP and substantially related with them (24).

CONCLUSION

From many years the role of actin binding protein in carcinogenesis have been studied but there are some reservations of understandings in what way they are involved and their biological significances. An extra worldwide approach that has been contained over the past few years to observe deviations in cancer cell development will in turn deliver a copious better understanding of the unlike regulatory procedures accountable for the incidence of metastasis. In all it is concluded that the regulation of actin is important in the progression of cancer cells and metastasis and there are many actin binding proteins like Arp2/3, WASP/WAVE, Tropomyosin, YAP, ECM and FASCIN-1 perform different functions and are involved in the development of cancer. In tumor cells the increased and decreased expression of these actin binding protein involves in progression of different types of cancer and metastasis.

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