

Cytoskeletal Molecules Play a Major Role in Cancer Progression

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Abstract

Abnormal cell behavior including uncontrolled proliferation and migration are evidenced in cancers which arise from multiple gene mutations mainly in somatic cells. Many changes can promote abnormal cell behaviors this review is mainly focusing on cytoskeletal based changes in relation to cancer. Cytoskeletal filaments including microtubules and microfilaments are highly dynamic structures mainly involved in cell movements and proliferation, whereas intermediate filaments are relatively permanent structures, which connect the cell to extra cellular matrix, provide a cellular network and help withstand mechanical stress.

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Introduction

The structure of eukaryotic cells depends on the regulation of its cytoskeleton. The cytoskeleton is a filamentous protein network containing three main molecules; microtubules, intermediate filaments and microfilaments. The cytoskeleton extends throughout the cytoplasm and connects to the plasma membrane. It continually responds to external stimuli and signals providing dynamic modification of its structural network. Cells that grow abnormally and acquire the ability to migrate and invade are the hallmark of metastatic cancers. Normal cell behavior regulated via the cytoskeletal filaments are altered in cancer. Several studies have demonstrated that alteration of cytoskeletal structures play a pivotal role in controlling cell behavior including in cancerous cells [1-3].

Microtubules

Microtubules are long, hollow tubes with highly dynamic structure formed by assembly of the tubulin heterodimer, alpha and beta subunits [4]. In animal cells microtubules mainly grow from the specialized single microtubule organizing centre called the centrosome, which contains centrioles and extends outward to reach the periphery. They mainly participate in transport of vesicles and organelles within cells and the formation of mitotic spindles during cell division. Structural instability, microtubule assembly and disassembly, is regulated by microtubule-associated proteins [5]. During cell division, dynamic instability of microtubules plays a major role in metaphase and anaphase by rapid assembly and disassembly respectively. In some cells microtubules provide relatively stable structures such as cilia and flagella.

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Multiple mutations in mitotic cells alter normal cell behavior and allow uncontrolled proliferation leading to cancer. Several microtubule specific drugs such as taxol can stabilise microtubules [6] whilst colchicine [7] can prevent microtubule polymerization. These agents have been used to control the growth of cancerous cells.

Intermediate filaments

Intermediate filaments are relatively permanent, rope like structures found in the nucleus and throughout the cytoplasm, linked with the extracellular matrix via cell junctions. They can be classified into different groups based on their location and their protein structures. Cytoplasmic intermediate filaments are (i) Keratin, found in epithelial tissues, (ii) Vimentin and Vimentin-related filaments, found in connective and muscles tissues and (iii) Neurofilaments, found in nerve tissues. Nuclear intermediate filaments nuclear lamins, are located in all animal cells and strengthen their nuclear envelope. Intermediate filaments provide mechanical strength and distribute stress when cells are stretched.

Almost 90% of cancerous cells arise from epithelial origin. Keratin is expressed in all types of epithelial cells. Different types of

keratin molecules are expressed in different cells [8] and keratin's expression pattern has been utilized as a diagnostic tool for many epithelial cancers. Recent studies demonstrated it as a useful marker for early cancer detection and prognosis.

Vimentin is highly expressed in normal mesenchymal cells whilst being absent in epithelial cells. Vimentin expression has been increased in many cancers with poor prognosis. Vimentin (mesenchymal marker) expression correlated with mesenchymal transition of epithelial cancer cells to metastatic cells [9].

Microfilaments

Microfilaments are thinner cytoskeletal structure made up of polymerized actin. Actin molecules are found in all eukaryotic cells and are involved in proliferation, migration and differentiation. Similar to microtubules microfilaments are also highly dynamic structures regulated by smaller actin regulatory proteins [10]. The actin regulatory proteins directly target the actin treadmilling process and regulate the length of the filaments by altering the ratio of globular monomeric G-actin and filamental F-actin. Cofilin, an actin depolymerising factor, is an important example of actin regulatory proteins that bind to F-actin and

control the length of the filaments by severing F-actin. Cofilin also binds to the G-actin monomer and sequesters monomers from the polymerising side [10-12]. Cofilin activity is tightly regulated via a serine/threonine protein kinase called LIM kinase [10] and slingshot phosphatase [13].

Discussion and Conclusion

During cell division microfilaments and associated motor proteins form a contractile ring and progress cytokinesis. Several studies have demonstrated that LIMK regulates cell cycle via regulation of actin cytoskeleton [14,15]. Dynamic alteration of microfilamental structure is very important in cell invasion, movement, adhesion and change in morphology. All these mechanisms are present in cancer cell progression. LIM kinase is highly expressed and activated in metastatic cancer cells compared to non-metastatic cells [16].

Controlling the F-actin formation may control cancer metastasis via controlling invasion and migration. We and others have demonstrated that by controlling actin filamental formation through inhibition of LIMK activity; tumour growth, invasion and migration can be prevented [2,16,17].

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