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Review

Exploiting the cytoskeletal filaments of neoplastic cells to potentiate a novel therapeutic approach

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ABSTRACT

Although cytoskeletal-directed agents have been a mainstay in chemotherapeutic protocols due to their ability to readily interfere with the rapid mitotic progression of neoplastic cells, they are all microtubule-based drugs, and there has yet to be any microfilament- or intermediate-filament directed agents approved for clinical use. There are many inherent differences between the cytoskeletal networks of malignant and normal cells, providing an ideal target to attain preferential damage. Further, numerous microfilament-directed agents, and an intermediate filament-directed agent of particular interest (withaferin A) have demonstrated *in vitro* and *in vivo* efficacy, suggesting that cytoskeletal filaments may be exploited to supplement chemotherapeutic approaches currently used in the clinical setting. Therefore, this review is intended to expose academics and clinicians to the tremendous variety of cytoskeletal filament-directed agents that are currently available for further chemotherapeutic evaluation. The mechanisms by which microfilament directed- and intermediate filament-directed agents damage malignant cells are discussed in detail in order to establish how the drugs can be used in combination with each other, or with currently approved chemotherapeutic agents to generate a substantial synergistic attack, potentially establishing a new paradigm of chemotherapeutic agents.

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1. Introduction

Cytoskeletal-directed agents have been a mainstay in chemotherapy due to their ability to readily interfere with the rapid proliferation of neoplastic cells. Malignant cells have a perturbed cytoskeleton due to the effects of dysplasia and subsequent anaplasia [1,2]. With so many alterations present in malignant cells, the cytoskeleton provides an ideal opportunity to attain preferential damage. Ever since vincristine began demonstrating clinical efficacy in the 1960s [3], the idea of disrupting the cytoskeleton of malignant cells during the mitotic phase has become widely considered in chemotherapeutic protocols. Along with paclitaxel (taxol) and the closely related docetaxel (taxotere) that make up the taxane drug family [4], vinca alkaloids (vinblastine, vincristine, vindesine, vinflunine and vinorelbine) have been used extensively to treat a variety of cancers, particularly hematological malignancies [2,5]. In recent years, the discovery of epothilones has furthered the development of cytoskeletal-directed agents as they have very similar *in vivo* effects to taxanes, but with higher efficacy, and reduced toxicity [6,7].

However, despite this apparent diversity of cytoskeletal-directed agents available to oncologists, all currently approved cytoskeletal-directed agents used in the clinical setting are essentially microtubule-directed agents. Although it is true that these compounds act by distinct mechanisms (taxanes and epothilones stabilize microtubules, while vinca alkaloids disrupt polymerization), they all have the same cytoskeletal target. Since microtubules are pivotal for mitosis, cell trafficking, and in some circumstances cell movement, inhibiting the dynamic instability of these polymers can be absolutely devastating for rapidly proliferating cells, henceforth ideal for disrupting tumorigenic growths [8,9]. While microtubule-directed agents have also been shown to induce apoptosis [10,11], they are inherently limited to one component of the cytoskeleton. The other potential targets, intermediate filaments and microfilaments, remain as elusive clinical prospects.

Cytoskeletal filaments are indeed viable targets to exploit in chemotherapy. Actin is inherently required for cell motility, cytokinesis, and many other processes vital for malignant cell stability [12–15]. Intermediate filaments such as keratins are often overexpressed in carcinomas due to the aberrant effects of associated oncogenes [16,17], and vimentin has been shown to be vital for cell survival in numerous experiments [18–20]. A substantial variety of microfilament-directed agents and one intermediate filament-directed agent in particular (withaferin A) have shown profound anticancer activity in a variety of cancer cell lines. Despite these compelling data, there has yet to be a clinically approved intermediate filament-directed or microfilament-directed agent used in cancer therapy. Therefore, this review is intended to expose academics and clinicians to the tremendous variety of cytoskeletal filament-directed agents that are currently available for chemotherapeutic evaluation (Fig. 1). It is hoped that such an analysis will provide enough data to warrant further *in vivo*, preclinical and eventual clinical trials of these compounds, thereby potentiating a new paradigm of chemotherapeutic agents.

2. Microfilaments as chemotherapeutic targets

Actin is a globular multi-functional protein that can be present as either a free monomer known as globular actin (G-actin), or as part of a microfilament polymer called filamentous actin (F-actin). In addition to being an ATPase that helps dictate its structure, actin is able to carry out more interactions than any other protein, allowing it to perform a tremendous diversity of functions necessary for cellular life, including chemotaxis and cytokinesis [21–24]. Actin polymerization is stimulated by nucleating factors such as the Arp2/3 complex, which mimics a G-actin dimer in order to stimulate G-actin nucleation. The Arp2/3 complex binds forming microfilaments to form new actin branches off existing polymers [23,24]. As an ATPase, actin binds ATP to stabilize microfilament formation, and hydrolysis of this nucleotide stimulates depolymerization [21]. The growth of microfilaments is regulated by thymosin and profilin; thymosin binds G-actin to buffer the polymerizing process, while profilin binds G-actin to exchange ADP for ATP, promoting monomeric addition to the barbed, plus end of F-actin [25]. Unlike many biological polymers, microfilaments are formed through non-covalent bonding, which enables filament ends to readily release or incorporate monomers [21]. Therefore, microfilaments rapidly remodel and change structure in response to environmental stimulus, giving such structures an assembly dynamic very similar to microtubules.

Along with microtubules, microfilaments are vital for successful cell proliferation. Shortly after the initiation of chromatid separation during anaphase, a contractile ring of non-muscle myosin II and microfilaments is assembled at the cell cortex [12,26]. Myosin II uses ATP hydrolysis to move along F-actin, constricting the cell membrane to form the cleavage furrow. The ingression of the cleavage furrow ultimately potentiates the abscission (the process by which the cell bodies are cleaved) which is entirely dependent on septin filaments beneath the cleavage furrow, as they provide structural support to ensure the completion of cytokinesis [14,26].

Due to the absolute requirement of microfilaments during cytokinesis, disrupting actin polymerization can exert profound effects on cellular structure. Cytokinesis inhibitors such as cytochalasin B disrupt the actin cytoskeleton and interfere with the formation of the contractile ring, as well as the development of the cleavage furrow [27,28]. Consequently, the cell is unable to divide, permeating a weakened cytoskeletal network. However, the cell is still able to initiate another mitotic event, continuing to form nuclei, and eventually becoming grossly enlarged and multinucleated [29,30]. Substantial multinucleation increases the likelihood of apoptosis, as it only takes a single nucleus to undergo programmed cell death before a chain reaction is triggered, culminating in the cell's destruction [1]. Further, the multinucleated cells have an increased cell volume and weakened cytoskeleton, making them more susceptible to physical agitation [31]. Preferential damage to malignant cells is facilitated by the fact that normal cells exposed to cytochalasin B exit the cell cycle and typically enter the G_0 phase until sufficient actin levels are restored [28]. As indicated by cultured BALB/c mouse mammary gland epithelial cells, normal mammary gland cells remain predominantly mono- or binucleate when exposed to cytochalasin B, while highly tumorigenic cell lines derived from mammary tumors become extensively multinucleated when cultured under the same conditions [32]. Further, cell lines derived from bladder, kidney, and prostate carcinomas become multinucleated when grown in cytochalasin B-supplemented medium, whereas cells from corresponding normal tissue remain mono- or binucleate under comparable conditions [29]. Therefore, only malignant cells that have lost the ability to enter the rest phase become grossly enlarged and multinucleated. Such cells are ideal targets for concomitant chemotherapy, as they have reduced cytoskeletal integrity, multiple nuclei, and even increased mitochondrial activity [31].

Actin is also of substantial importance to cancer cell migration. Carcinomas are the most prevalent form of cancer, constituting ~85% of all cases annually worldwide [1]. It has been well documented that dedifferentiated epithelial cells will undergo an epithelial–mesenchymal transition (EMT) in order to readily detach and migrate toward nearby vasculature [33–35]. This transformation into a motile cell type is typically only reserved for embryonic development and wound healing [1], and is a marked sign of cancer progression. Since these transformed cells are dependent on the recruitment of matrix-degrading proteases to reach endothelial tissue, it has been postulated that potent protease inhibitors may be able to significantly delay or even reduce the rate at which metastasis is observed [33,34]. However, transformed epithelial cells are also capable of amoeboid migration that is typically seen in lymphocytes and neutrophils. In this type of migration, cell–substrate adhesions are weak, resulting in the cell presenting a rounded morphology. When rounded cells migrate through the extracellular matrix (ECM), they change shape and squeeze themselves into

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