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Review article

Taking aim at a dynamic target: Noscapinoids as microtubule-targeted cancer therapeutics

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ABSTRACT

Noscapine and its synthetic derivatives called noscapinoids have been shown to possess potential anticancer properties. These alkaloids target microtubules and inhibit cell proliferation. Noscapinoids are microtubule poisons that induce minor alterations in the innate dynamic instability of microtubules leading to mitotic arrest and cell death. Over the past decade, a number of noscapine derivatives have been synthesized that, compared to the parent compound, show superior anticancer potential, enhanced tumor specificity and tumor regression, and little or no toxicity to normal tissues. Based on their successive synthetic modifications at different points in the scaffold structure of noscapine, aided by computational design and structure–activity relationship studies, the derivatives of noscapine have been classified into different "generations" based on modifications. Several studies have reported the potential to develop noscapinoids as anticancer drugs. Increasing their tumor specificity - either through antibody conjugation or nanoparticle-based carriers - may facilitate the progression of maytansinoid-based cancer drugs to the clinic.

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Introduction

French chemist Pierre Robiquet first isolated noscapine, a cough-depressant benzylisoquinoline alkaloid, in 1817, and it became known as *narcotine* until the late 1950s [1]. Noscapine's ability to interact with microtubules and suppress the dynamic instability of microtubules and thereby inhibit cell proliferation prompted a number of studies on its potential as an anticancer agent [2]. Over the past decade, numerous derivatives of noscapine have been synthesized and their anti-proliferative mechanism of action, ability to inhibit tumor progression in xenograft animal models, tumor specificity, and side effects evaluated [3].

Microtubules, the target protein of noscapine, are cylindrical, linear, cytoskeletal polymers composed of α and β tubulin heterodimers [4]. Microtubules exhibit an intrinsic behavior called *dynamic instability*, shifting frequently between periods of growth and shortening phases [5]. Microtubules play a number of roles in various cellular functions, including cell division, intracellular transport, and the positioning of cellular organelles [4]. During normal mitosis, microtubules segregate sister chromosomes into daughter cells through a spatially and temporally synchronized mechanism mediated by cell cycle checkpoints [4]. This crucial role in cell division makes microtubules an attractive target for cancer chemotherapy. A number of tubulin-binding molecules with anticancer potential have been discovered in recent years. These agents interact with microtubules through diverse mechanisms to inhibit cancer cell proliferation [6]. For example, compounds such as vinca alkaloids [7] and maytansine [8] bind at growing microtubule tips and suppress dynamic instability. Taxol [6,7], taccalonolide [9], and taxol derivatives suppress microtubule dynamics by stabilizing the lateral interactions between protofilaments [7]. Many of these drug molecules are thought to mimic cellular proteins that stabilize or destabilize microtubule dynamics by binding to tubulin and microtubules. For example, end binding protein 1 (EB1) and the cytoplasmic linker protein CLIP-170 are known to stabilize microtubule dynamics [10], whereas cellular proteins such as stathmin [11] and G proteins increase microtubule dynamics [12].

Suppression of dynamic instability arrests cell cycle progression by adversely affecting the formation and maintenance of a functional mitotic spindle [7]. In fact, even minor perturbations in microtubule dynamics have been reported to induce mitotic arrest [13]. Drug-induced alterations of microtubule dynamics are known to induce a loss of tension across sister kinetochores at the metaphase plate [13,14]. (The tension is generated during metaphase when microtubules attach properly to the kinetochores of sister chromosomes). The loss of tension activates checkpoint proteins such as Mad2 and BubR1, which prevent progression of the cell cycle to anaphase by inhibiting the activation of the anaphase promoting complex, leading to cell cycle arrest [14]. Though chemically diverse, microtubule-targeted compounds are characterized by their ability to disrupt the normal assembly dynamics of the mitotic spindle, thereby inhibiting cell division at the metaphase/anaphase transition [7].

Noscapine, a microtubule-modulating agent

Noscapine ((3S)-6,7-Dimethoxy-3-((5R)-5,6,7,8-tetrahydro-4-methoxy-6-methyl-1,3-dioxolo(4,5-g) isoquinolin-5-yl)-1(3H)-isobenzofuranone; Fig. 1) is a phthalideisoquinoline alkaloid originally isolated from plants of the papaveracea family, including *papaver somniferum* (opium poppy) [15]. Also known as narcotine, nectodon, nospen, and anarcotine, noscapine has been used as a cough depressant in several clinical formulations [14,15].

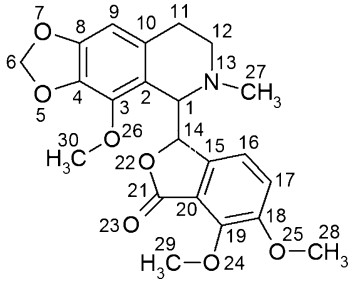

Fig. 1. Molecular structure of noscapine with numbering of carbon atoms. Noscapine structure consists of two ring systems, isoquinoline and isobenzofuranone, linked by a rotatable C–C bond between two chiral centers.

The anticancer properties of noscapine have been well documented in a number of studies. It induces mitotic arrest and programmed cell death in several types of cancer cells. In glioma cells, for example, it promotes apoptosis through a C-Jun-N-terminal kinase pathway [16]. In colon cancer cells, noscapine induces mitotic arrest and cell death through a p53- and p21-dependent mechanism [17]. It was found to promote cell death in both apoptosis-resistant and -prone leukemia cell lines [18]. It suppresses the growth of xenograft tumors (non-small cell lung cancer) in mice [19]. From a clinical point of view, noscapine is distinguished from many other microtubule-targeted agents by its lack of considerable cytotoxicity to normal cells [20]. Moreover, it has a good pharmacokinetic and absorption, distribution, metabolism, and excretion (ADME) profile [20] and does not produce major organ toxicities [20]. Noscapine interacts with tubulin and microtubules in a distinctive manner [21,22]. This review focuses on the current understanding of noscapine's mechanism of action and the development of novel noscapine derivatives (collectively called noscapinoids). The review concludes with future perspectives for noscapine's potential as an effective anticancer drug.

Interactions of noscapine with tubulin and microtubules

Screening for microtubule-targeted agents with functional groups similar to colchicine, podophyllotoxin, and like agents, Harish Joshi's group at Emory University, Atlanta, first reported noscapine's microtubule-interfering action and the correlation between mitotic arrest and microtubule disorganization caused by this alkaloid [22]. Abnormal, multipolar spindle microtubules were observed in noscapine-treated HeLa cells. The cells thus arrested in mitosis eventually underwent apoptosis. While investigating noscapine's molecular mechanism of action, it was found to bind to tubulin, as evidenced by a concentration-dependent quenching of the intrinsic tryptophan fluorescence of tubulin [22]. The mechanism of mitotic arrest induced by noscapine was later discovered by the same group, in collaboration with Leslie Wilson's laboratory at the University of California, Santa Barbara. They found that noscapine arrests cancer cells by altering the dynamic instability of microtubules, primarily by increasing the attenuated state [23]. Specifically, noscapine (50 μM) increases the time microtubules spent in "attenuated state" (a phase in the dynamic instability where no detectable growth or shortening happens). In addition, noscapine substantially reduces the "catastrophe frequency" (occurrences of rapid shortening of microtubules) and increases the "rescue frequency" (occurrences of transition from shortening phase to growth phase). The net effect of noscapine on dynamic instability is suppression of the overall dynamicity of microtubules by ~60% [23].