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Noscapinoids: A new Class of Anti-Cancer Drugs Demand Biotechnological Intervention

Harish C. Joshi

Emory University, School of Medicine, Department of Cell Biology, GA, USA

Microtubules (MTs) are cytoskeletal components that play a critical role in many cellular processes such as maintenance of cell shape and polarity, intracellular transport of vesicles and organelles, and cellular motility. During cell division, MTs form a bipolar microtubule (MT) array, called the mitotic spindle responsible for the accurate distribution of chromosomes into two daughter cells. MTs are assembled from alpha- and beta-tubulin heterodimers, and are highly dynamic structures that alternate between periods of growth and shortening. This dynamic instability property is crucial for MTs to carry out many of their cellular functions. Disruption of MT dynamics can lead to the formation of abnormal mitotic spindles, thereby preventing the normal cell proliferation. The critical role that MTs play in cell division makes them a very suitable target for the development of chemotherapeutic drugs against the rapidly dividing cancer cells. The effectiveness of MT-targeting drugs has been validated by the successful use of several vinca alkaloids and taxanes for the treatment of a wide variety of human cancers. These agents inhibit or promote the polymerization of tubulin respectively, halt mitosis of rapidly dividing cells, induce apoptosis, and are reasonably effective in cancer chemotherapy. As a testament to this, USFDA has approved the use of taxanes such as paclitaxel and taxotere as a first line chemotherapy for ovarian and breast cancers and vincas such as vinblastine, vincristine, and vinorelbine for some hematological pathologies. However, drug resistance is a common problem with repeated and prolonged administration of these agents, possibly owing to the amplification of a membrane glycoprotein involved in efflux of the drug. Moreover, these anti-MT agents are frequently toxic to normal tissues and are effective only for certain types of cancers. Despite the current cumbersome intravenous slow infusions, requiring multiple hospital visits, uncomfortable side effects of the gastro intestinal and immune systems, neutrocytopenia, and peripheral neuropathies, the first generation MT drugs, vincas, taxanes, epothilones, have proven that MTs are valuable targets for anti-cancer therapy. Noscapine and its promising derivatives now offer the prospect of a nicer, kinder, and gentler opium derived non-narcotic oral safe class of anti-cancer drugs that can be taken at home. Noscapine has already begun its progress into the pipeline of clinical drug development. New more effective and even targeted derivatives are under development in our group, and we hope many more will follow suite. In addition, biotechnological interventions are underway to obtain improved production of the compound and efforts to metabolically engineer the biosynthetic pathways for enhancing yield. Another challenge these useful drugs face, is their poor solubility in biocompatible solvents. As a result they are solubilized in unfriendly carriers such as Cremphor EL that runs the risk of anaphylactic shocks and medical emergencies. Hence, there is an urgent need for new and better chemotherapeutic drugs for cancer treatment.