Editorial

Anticancer Natural Compounds: Molecular Mechanisms and Functions Part II

In spite of enormous success achieved by the cancer biologists and clinical oncologists alike for the last decades, cancers still presents a great challenge for the researchers and suffering for the patients. While basic mechanisms underlying tumor initiation and progression are unraveling as we speak, as well as novel therapeutic strategies often appear in clinical practice the tumors defend themselves with acquired resistance to therapies using the whole arsenal of their hallmarks. Cancer cells exhibit limitless proliferative potential, sustain self-sufficiency in growth signals, resist anti-growth signals and evade apoptosis induced by the stress signals including therapeutic drugs, stimulate the growth of blood vessels to supply nutrients to tumors, exert their ability for invasion and metastasis, while evading the immune system defense and inducing local chronic inflammation, exhibit deregulated metabolism, and dramatically alter whole genome stability through mutational and epigenetic mechanisms. Natural compounds derived from plants, microorganisms and marine life forms have gained a considerable interest among cancer researchers for the potential to affect multiple cancer hallmarks. Furthermore, many existing anticancer compounds used in clinic today originally derived from the natural habitats. In the present Thematic Issue “Anticancer Natural Compounds. Molecular Mechanisms and Functions”, the investigators from around the world present their views on the role for natural compounds to combat cancer cells *in vitro* and *in vivo*, describing some successful stories leading to the clinical trials, therefore supporting high hopes that natural approaches could be beneficial to combat cancer disease.

The research groups led by Drs. Natalia Bailon-Moscoso and Luis Miguel Guaman Ortiz from the Universidad Tecnica Particular de Loja (Ecuador) in collaboration with Prof. Edward Ratovitski (Johns Hopkins University School of Medicine, Baltimore, MD, USA) emphasize the key cellular responses to natural compounds underlying cell cycle arrest and multiple non-apoptotic cell death mechanisms (e.g. autophagy, necroptosis, paraptosis, parthanatos, and mitotic catastrophe). A number of natural compounds that induce cell cycle arrest have proven effective for killing cancer cells *in vitro*, *in vivo* and in clinical settings. Significant advances that have been recently made in the understanding of molecular mechanisms underlying the cell cycle regulation using the chemotherapeutic agents is of great importance for improving the efficacy of targeted therapeutics and overcoming resistance to anticancer drugs, especially of natural origin, which inhibit the activities of cyclins and cyclin-dependent kinases, as well as other proteins and enzymes involved in proper regulation of cell cycle leading to controlled cell proliferation. Cell death is often regulated by multiple molecular pathways and mechanism, including apoptosis, autophagy, and necroptosis. The molecular network underlying these processes is often intertwined and one pathway can dynamically shift to another one acquiring certain protein components, in particular upon treatment with various drugs.

The researchers led by Prof. Edgar J. Paredes-Gamero (H.V.F. Torquato and collaborators) at the Universidade Federal de São Paulo (Campus São Paulo, São Paulo, Brazil) define the roles of natural bioactive compounds from medicinal plants in cancer treatment, as an attractive alternative to other treatments because they exhibited lower toxicity and higher selectivity against cancer cells. Authors focus on the possible application of bioactive molecules obtained from plants against more primitive cell populations in cancers, cancer stem cells. Cancer stem cells are present in several kinds of tumors and are responsible for recurrences and metastases. Common anti-cancer drugs exhibit lower effectiveness against cancer stem cells because of their biological features. However, recently discovered natural phytometabolites exert cytotoxic effects on this rare population of cells in cancers. Therefore, this review presents the latest research on promising compounds from plants that can act as anti-tumor drugs and that mainly affect stem cell populations in cancers.

Finally, Prof. Edward A. Ratovitski (Johns Hopkins University School of Medicine, Baltimore, MD, USA) shows how numerous natural compounds from the diverse organisms affect tumor cells through multiple epigenetic mechanisms, including transcriptional factors, chromatin-accessory proteins, DNA methyltransferases, histone acetylases and deacetylases, histone methylases and demethylases, as well as numerous microRNAs. The current review will describe the latest achievements in using naturally produced compounds targeting epigenetic regulation of gene expression *in vitro* and *in vivo* to generate novel anticancer therapeutics.

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