Abstract

Targeted Anticancer Strategies with Garlic Derivatives †

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† Presented at the Natural Products and the Hallmarks of Chronic Diseases—COST Action 16112,
Published: 19 April 2019
Keywords: Diallyl compounds; tubulin; Bcl-2; autophagic flux; apoptosis

Diallyl polysulfides from edible plants have been widely investigated in cancer research holding the promise of a translational application. Generally recognized as inducers of mitotic arrest and cell death, yet their activities appear broad, without specific intracellular targets. Here we suggest their potential as targeted agents and cancer types as suitable responders, taking the garlic-derived diallyl tetrasulfides (DATTS) and its most effective hemi-synthetic derivative di-benzyl tetrasulfide (DBTTS) as lead compounds [1–4]. We discovered DATTS/DBTTS as reversible tubulin binders, via redox modulation of the tubulin thiols. Translating our investigations to cellular models, we selected cancer types of the gastrointestinal tract (colorectal cancer, CRC) and the blood (acute forms of leukemia), being both highly proliferating and exposed in vivo to appropriate and stable concentrations of sulfur compounds. In both cell types, DATTS/DBTTS binding compromises the microtubule machinery, thereby inducing mitotic arrest and apoptosis [1–4]. Of note, a higher expression of genes coding specific tubulin isoforms in KRAS-mutated CRC SW480 and SW620 correlates with faster cell proliferation and the increased susceptibility to these compounds vs. the most resistant BRAF-mutated HT-29 [1]. The resistance in HT-29 associated with the impairment of the autophagic flux concomitant with the prolonged mitotic block and characterized by p62 protein accumulation. Genetic p62 inhibition restores sensitivity. We confirmed the translational potential of DBTTS in 3D CRC models (in vitro: spheroids and colony formation assay; and in vivo: zebrafish xenografts) [1]. In both cell types, anti-apoptotic Bcl-2 protein members undergo phospho-modulation. In hematological cancer, Bcl-2 proteolysis/inhibition promotes cell death [2–4]. In line, Bcl-2 over-expression makes the cells more resistant; vice versa, isogenic cell lines expressing Bcl-2 mutated in the phosphorylatable residues are again sensitized to the treatment, suggesting Bcl-2 proteins as critical stress sensors and transducers. Overall, we recommend components of the microtubule network, differential autophagic capacities, and Bcl-2 proteins modulation as essential factors of vulnerabilities to prioritize DATTS/DBTTS treatment.

Funding: C.C. and E.Y.E. were supported by a grant from Télévie Luxembourg. This research is supported by the “Recherche Cancer et Sang” foundation, “Recherches Scientifiques Luxembourg” association, “Een Hærrz fir kriibskrank Kanner” association, Action LIONS “Vaincre le Cancer” association and Télévie Luxembourg. This research is also supported by National Research Foundation (NRF) [grant number 019R1A2C1009231] and by a grant from the MEST of Korea for Tumor Microenvironment Global Core Research Center (GCRC) [grant number 2011-0030001]. Support from Brain Korea (BK21) PLUS program and Creative-Pioneering Researchers Program at Seoul National University [Funding number: 370C-20160062] are acknowledged. This article is based...
upon work from COST Action NutRedOx-CA16112 supported by COST (European Cooperation in Science and Technology).

Conflicts of Interest: The authors declare no conflict of interest.

References


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