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Extended Abstract

Targeted Anticancer Strategies with Garlic Derivatives †

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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 phosphorylable 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.

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