Anti-cancer potential of synergistic phytochemical combinations is influenced by the genetic profile of prostate cancer cell lines

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Abstract

Introduction: Despite strong epidemiological evidence that dietary factors modulate cancer risk, cancer control through dietary intervention has been a largely intractable goal for over sixty years. The effect of tumour genotype on synergy is largely unexplored.

Methods: The effect of seven dietary phytochemicals, quercetin (0-100 μM), curcumin (0-80 μM), genistein, indole-3-carbinol (I3C), equol, resveratrol and epigallocatechin gallate (EGCG) (each 0-200 μM), alone and in all paired combinations om cell viability of the androgen-responsive, pTEN-null (LNCaP), androgen-independent, pTEN-null (PC-3) or androgen-independent, pTEN-positive (DU145) prostate cancer (PCa) cell lines was determined using a high throughput alamarBlue® assay. Synergy, additivity and antagonism were modelled using Bliss additivism and highest single agent equations. Patterns of maximum synergy were identified by polygonogram analysis. Network pharmacology approaches were used to identify interactions with known PCa protein targets.

Results: Synergy was observed with all combinations. In LNCaP and PC-3 cells, I3C mediated maximum synergy with five phytochemicals, while genistein was maximally synergistic with EGCG. In contrast, DU145 cells showed resveratrol-mediated maximum synergy with equol, EGCG and genistein, with I3C mediating maximum synergy with only quercetin and curcumin. Knockdown of pTEN expression in DU145 cells abrogated the synergistic effect of resveratrol without affecting the synergy profile of I3C and quercetin.

Discussion: Our study identifies patterns of synergy that are dependent on tumour cell genotype and are independent of androgen signaling but are dependent on pTEN. Despite evident cell-type specificity in both maximally-synergistic combinations and the pathways that phytochemicals modulate, these combinations interact with similar prostate cancer protein targets. Here, we identify an approach

that, when coupled with advanced data analysis methods, may suggest optimal dietary phytochemical combinations for individual consumption based on tumour molecular profile.Graphical abstract.

Keywords: Bliss; network pharmacology; pTEN loss; phytochemicals; prostate cancer; synergistic combinations.