SATB2 suppresses invadopodia formation in colorectal cancer cells via palladin inhibition.

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Invadopodia are specialized actin-based microdomains of the plasma membrane that combine adhesive properties with matrix degrading activities. Proper functioning of the bone, immune, and vascular systems depend on these organelles, and their relevance in cancer cells is linked to tumor metastasis. The elucidation of the mechanisms driving invadopodia formation is a prerequisite to understanding their role and ultimately to controlling their functions. Special AT-rich sequence-binding protein 2 (SATB2) was reported to suppress tumor cell migration and metastasis. However, the mechanism of action of SATB2 is unknown. Here, we show that SATB2 inhibits invadopodia formation in HCT116 cells and that the molecular scaffold palladin is inhibited by exogenous expression of SATB2. To confirm this association, we elucidated the function of palladin in HCT116 using a knock down strategy. Palladin knock down reduced cell migration and invasion and inhibited invadopodia formation. This phenotype was confirmed by a rescue experiment. We then demonstrated that palladin expression in SATB2-expressing cells restored invasion and invadopodia formation. Our results showed that SATB2 action is mediated by palladin inhibition and the SATB2/palladin pathway is associated with invadopodia formation in colorectal cancer cells.

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Polyphenols act synergistically with Doxorubicin and Etoposide in leukaemia cell lines

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Background: The study aimed to assess the effects of polyphenol when used in combination with doxorubicin and etoposide, and determine whether polyphenols sensitized leukaemia cells, causing cell-cycle arrest, inhibition of cell proliferation and induction of apoptosis. The rationale being that in some solid tumours, polyphenols have been shown to sensitize cells to apoptosis and/or cell-cycle arrest, potentially reducing doses, whilst maintaining efficacy.

Method: Quercetin, apigenin, emodin, rhein, cis-stilbene were investigated alone and in combination with etoposide and doxorubicin in two lymphoid (Jurkat and CCRF-CEM) and two myeloid (THP-1 and KG-1a) leukaemia cells lines. Measurements were made of ATP levels (CellTiter-Glo® assay), cell-cycle progression (propidium iodide (PI) staining and flow cytometry) and apoptosis (NucView-caspase-3 assay and Hoechst 33342/PI staining). The effects of these combinations on the apoptotic pathway (caspases-3, -8 and -9 Glo® luminescent assays), glutathione levels (GSH-Glo™-glutathione assay and cell tracker™ green-5-chloromethylfluorescein-diacetate-glutathione staining) and DNA damage (Alexa Fluor® 647 Mouse anti-H2AX staining) were also determined.

Results: Doxorubicin and etoposide in combination with polyphenols synergistically reduced ATP levels, induced apoptosis and increased S- and/or G2/M-phase cell-cycle arrest in lymphoid leukaemia cell lines. In the myeloid cell lines doxorubicin and etoposide displayed differential effects. Doxorubicin had a synergistic or additive effect when combined with quercetin, apigenin, emodin, and cis-stilbene, but had an antagonistic effect when combined with rhein. Combination treatment caused a synergistic down regulation of glutathione (GSH) levels and increased DNA damage, driving apoptosis via caspase 8 and 9 activation. However, in myeloid cells were an antagonist effect this was associated with an up-regulation of GSH levels, a reduction in DNA damage and apoptosis.

Conclusion: Doxorubicin and etoposide activity can be enhanced by polyphenols, particularly in lymphoid leukaemia cells, although effects were strongly dependent on type of cell line, with some interactions were antagonistic in myeloid cell lines.