Identification of The Molecules and Mode of Action Involved In The Melanoma Inhibitory Effect of Green Tea Polyphenol EGCG

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Summary

(−)-Epigallocatechin-3-*O*-gallate (EGCG) has been shown to induce anticancer activity through a cell surface receptor, 67-kDa laminin receptor (67LR). However, the underlying molecular mechanisms of EGCG remain obscure. In this study, by performing functional genetic screening of EGCG, we identified protein phosphatase 2A (PP2A) as a critical factor in suppression of melanoma cell proliferation. EGCG activated PP2A through 67LR and knockdown of PP2A abolished EGCG-elicited anti-melanoma activity. Moreover, we also found SET, a potent inhibitory protein of PP2A, overexpressed on malignant melanoma. Silencing of SET enhanced 67LR/PP2A signal shows significant growth inhibition activity. Collectively, our results demonstrated that EGCG inhibits melanoma growth by activating PP2A through 67LR and targeting SET may enhance the anti-melanoma activity of EGCG.

Introduction

(−)-Epigallocatechin-3-*O*-gallate (EGCG) has been shown to be the most active and major polyphenolic compound from green tea. The mechanisms of action of EGCG have been extensively investigated and it has been reported that EGCG induces anticancer activity by dephosphorylating myosin II regulatory light chain (MRLC)[1] through a cell surface EGCG receptor, 67-kDa laminin receptor (67LR)[2]. However, the underlying molecular mechanisms of EGCG remain obscure.

Materials and methods

In this study, to understand the underlying molecular mechanisms of anticancer activity of EGCG, we applied a functional genetic screening—genetic suppressor element methodology (GSE) in mouse melanoma cell (B16) model to directly identify genes mediating cell sensitivity to EGCG.

Results and discussion

The functional genetic screening revealed that protein phosphatase 2 A (PP2A) plays a pivotal role in the anti-melanoma activity of EGCG. Interestingly, PP2A is abnormally elevated in human malignant melanoma relative to normal human skin. EGCG activated PP2A time-dependently through 67LR. Moreover, tumor growth was significantly retarded in EGCG-administered mice implanted with the B16 cells harboring a control shRNA and showed a significant survival benefit, whereas tumor growth was not affected by EGCG in the mice implanted with PP2A-ablated B16 cells and showed none effect on survival. Interestingly, we also found SET, a potent inhibitory protein of PP2A, overexpressed on malignant melanoma. Silencing of SET enhanced 67LR/PP2A signal shows significant tumour growth inhibition activity and increased survival rate. Taken together, our results demonstrated that EGCG inhibits melanoma growth by activating PP2A through 67LR and targeting SET may enhance the anti-melanoma activity of EGCG.

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