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67-kDa laminin receptor and cGMP induced cancer-selective apoptosis

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Background

EGCG ((−)-epigallocatechin-3-O-gallate), a polyphenol in green tea, induces apoptotic cell death in cancer cells without affecting normal cells and several clinical trials have been carried out to evaluate its potential value [1,2]. 67-kDa laminin receptor (67LR) has been identified as an EGCG receptor [3]. It has recently been demonstrated that overexpressed 67LR in multiple myeloma (MM) mediates EGCG-induced cancer-specific apoptosis [4-6]. In this study, we revealed that cGMP acts as a cell death mediator of the EGCG-induced anti-MM effect through acid sphingomyelinase (ASM) activation. In this apoptosis

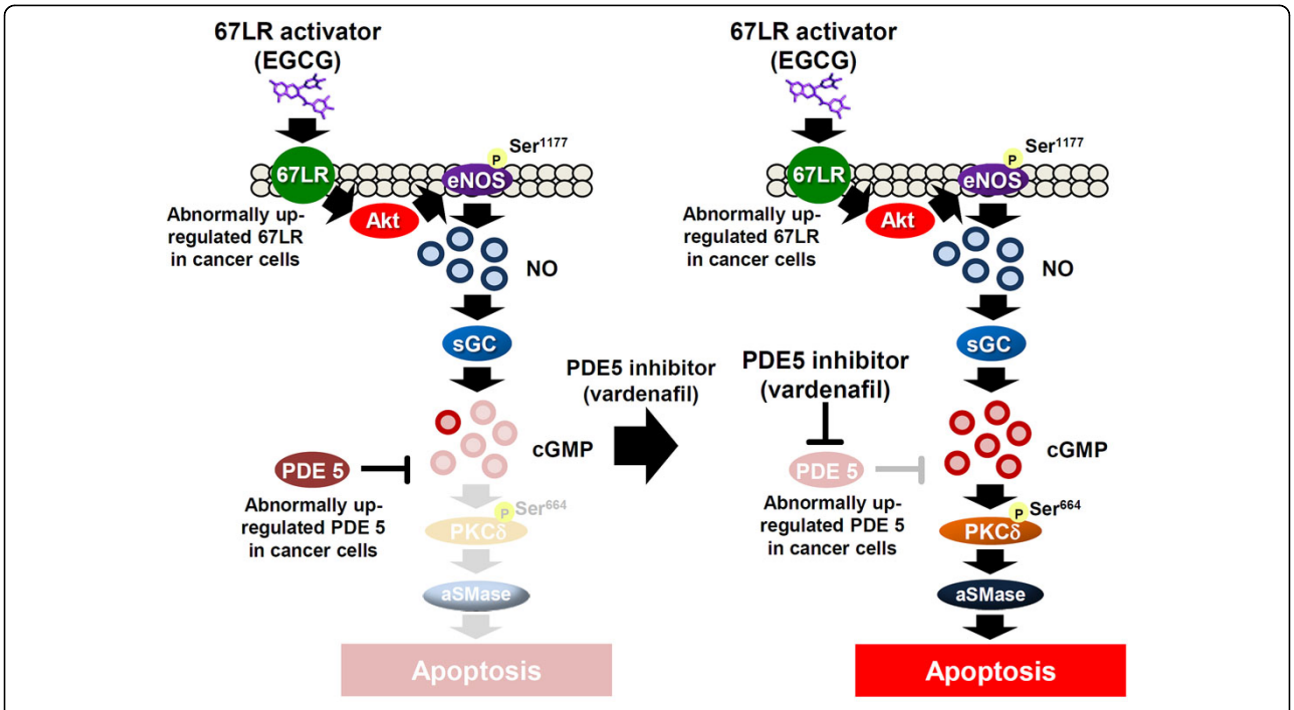

Figure 1 EGCG activates the endothelial nitric oxide synthase (eNOS)/cGMP axis via cancer-overexpressed 67LR (A) EGCG induced eNOS activation through 67LR.

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pathway, EGCG activated the endothelial nitric oxide synthase (eNOS)/cGMP axis, a well-known mechanism in vascular homeostasis via cancer-overexpressed 67LR. We also demonstrated that cGMP negative regulator, phosphodiesterase 5 (PDE5), was overexpressed in MM cells, and vardenafil, PDE5 inhibitor synergically enhanced the anti-MM effect of EGCG (see Figure 1). This regimen in combination killed MM via overexpressed 67-kDa laminin receptors without affecting normal PBMCs.

Conclusion

In this study, we demonstrate 67LR activated the peculiar apoptotic signalling eNOS/NO/ cGMP/protein kinase Cδ (PKCδ) pathway. Furthermore, we show the upregulation of cGMP is rate-determining process of this cell death pathway. We demonstrate cancer overexpressed negative regulator of cGMP, PDE5 attenuates the cGMP-dependent cell death induced by EGCG. Vardenafil, one of the PDE5 selective inhibitors used for treating erectile dysfunction potentiates anti-cancer effect of EGCG. These results demonstrate that cGMP elevation caused by targeting the overexpressed 67LR and PDE5 in cancer cells may be a useful approach for cancer-specific chemotherapy.

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