Mechanistic study on antiangiogenic effect of green tea component EGCG

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Angiogenesis, a process of construction of new blood capillaries, is crucial for tumor progression and metastasis. Previous studies demonstrated that a component of green tea catechins, epigallocatechin-3-gallate (EGCG) suppressed tumor angiogenesis and subsequent tumor growth. However, the detailed action mechanism of EGCG on antiangiogenic effect, especially distribution of EGCG in angiogenic endothelial cells, has not been clear. In the present study, distribution of EGCG was investigated by using the fluorescence-labeled EGCG derivative (EGCG-TG).

Two EGCG derivatives, *cis*- and *trans*-6-(5-aminopentyl)-5,7 -deoxyepigallocatechin gallate (*cis*- and *trans*-APDOEGCG) were firstly synthesized by my collaborators, and the antiangiogenic effect of these EGCG derivatives was confirmed. When the effect of *cis*- and *trans*-APDOEGCG on HUVEC proliferation was examined, the EGCG derivatives showed enhanced anti-proliferative effect compared with original EGCG at over 30 μM, whereas all compounds did not show any anti-proliferative effect at 1 μM. Then, by using this 1 μM concentration of the derivatives, other antiangiogenic effects such as HUVEC migration, invasion, and tube formation were examined. As the result, both EGCG derivatives showed stronger inhibitory effect on HUVEC migration, invasion and tube formation than non-derivatized EGCG. Furthermore, these derivatives changed distribution of *F*-actin and subsequent morphology of HUVECs. These results suggested that that derivatization of EGCG retained antiangiogenic effect without loss of the activity. Thus, it could be thought that the action mechanism of these derivatives was similar to EGCG. Finally, EGCG-TG was synthesized by conjugating fluorescent TokyoGreen to *cis*-APDOEGCG and the distribution of it in HUVECs was investigated. As the result, the abundant fluorescence was observed in the cells after a 3-h incubation, and was localized in not only cytoplasm but also mitochondria. The present study demonstrated that EGCG was incorporated into HUVECs, and a portion of them was interacted with mitochondria and then showed antiangiogenic activity.