Plant flavonoids prevent cancer progression through suppression of new blood vessel formation

Flavonoids are a sub-family of polyphenolic compounds. They are abundantly found in plants and known to have inhibitory properties in the initiation, promotion and progression of invasive cancers. Cancer progression is a complex process. It is mainly governed by altered-regulation of many biological pathways. In normal healthy cells, the level of growth factors and other molecules influencing cell proliferation, differentiation and eventual death are precisely maintained. Therefore, these cellular events continue to take place in a strictly-controlled environment. This ensures that the cells do not undergo unnecessary cell division leading to cancer initiation. In contrast, cells in cancers divide continuously beyond its own control.

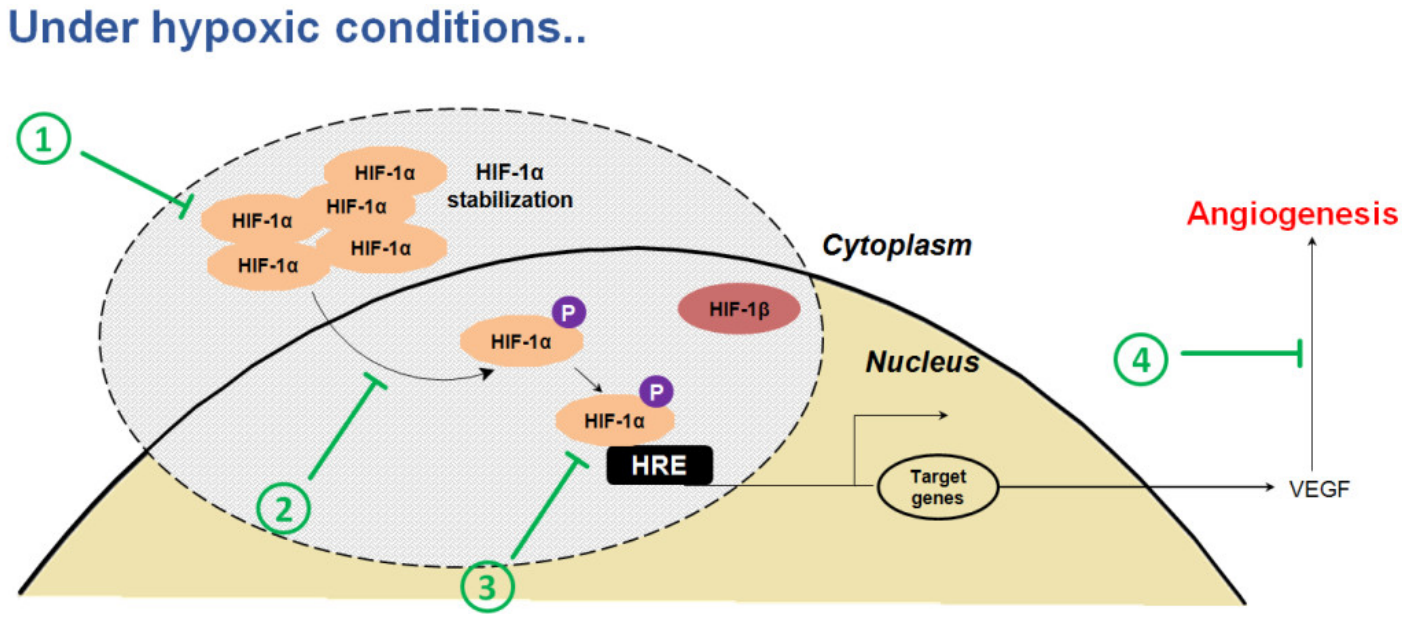

Fig. 1. HIF-1? stabilization and VEGF synthesis in a hypothetical cancer cell.

This will eventually resulted in failure of cancer cells to respond to inhibitory signals to stop the uncontrolled-cell proliferation. Solid cancers grow into a tumor mass as a result of extensive cell division. The cancer cells are in need of excessive supply of nutrients in order to acquire the energy required for cell division. However, the blood vessels supplying nutrients to the solid tumor are mostly found at the periphery of the tumor. Therefore, nutrients and oxygen are poorly penetrated into the center of a solid tumor. This creates a low-oxygen (hypoxic) environment in the cancer cells. Development of a hypoxic environment activates a number of pathways which favor the survival of cancer cells under low-oxygen levels. One of such survival mechanisms is the stabilization of hypoxia-inducible factor-1? (HIF-1?). As shown in the Fig. 1., this will ultimately

trigger the formation of vascular endothelial growth factor (VEGF). VEGF is considered as the most important indigenous growth factor required for the formation of new blood vessels (angiogenesis). Therefore, blocking of HIF-1? stabilization and subsequent VEGF formation is an attractive target of the development of novel anti-cancer agents.

Many studies have shown that flavonoids possess the capacity to prevent the angiogenesis. It has also been shown that flavonoids act at multiple points of the angiogenesis induction pathways. As shown in the figure, these inhibitory steps include (1) the stabilization of HIF-1?, (2) nuclear translocation of HIF-1?, (3) HIF-1 dimerization and (4) inhibition of VEGF. These studies have been conducted using human cancer cell lines such as breast, colon, prostate, lung and ovarian incorporating more than 25 naturally occurring-flavonoids. Further, these findings have been confirmed using suitable mice models as well. For example, epigallocatechin-3 gallate (EGCG), a flavonoid found in tea leaves inhibits HIF-1? and VEGF in breast, colon and lung cancer cells. Further, these effects have also seen in human pancreatic cancer bearing-mice as well. Altered expression of HIF-1? and excess VEGF is more frequently found in cancer cells compared to normal healthy cells. Therefore, these compounds also receive the attention to be developed as a selective anticancer agents. Angiogenesis is also essential for the metastasis (spreading) of primary cancers to a secondary location. Therefore, inhibition of angiogenesis will have an impact on the prevention of metastasis as well. Even though the work so far is promising, further experiments to explain the precise molecular mechanisms and preclinical testing to confirm the efficacy and safety of flavonoids are needed before proceeding these anti-angiogenic candidate compounds into clinical trials.

Publication

Regulation of Hypoxia-inducible Factor-1? and Vascular Endothelial Growth Factor Signaling by Plant Flavonoids.
Fernando W, Rupasinghe HP, Hoskin DW.
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