FUCOIDAN INHIBITS TUMOR ANGIOGENESIS THROUGH SUPPRESSION OF HIF-1α/VEGF SIGNALING UNDER HYPOXIA

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Introduction: The hypoxia, a characteristic feature of most advanced solid tumors, can induce tumor angiogenesis by activating hypoxia-inducible factors-1 (HIF-1α), a transcriptional factor. Fucoidan extracted from brown alga, exhibits several beneficial functions, including anti-inflammatory and anticancer activities. Recently, the low molecular weight fucoidan (LMWF) has been reported to have a greater anticancer activity. However, the effects of LMWF on the tumor angiogenesis and the role of HIF-1α under hypoxia remain unclear.

Objectives: To investigate whether LMWF attenuates the angiogenesis in hypoxic human bladder cancer cells (T24) cells and tumor, and further studied the involvement of HIF-1α-regulated signaling pathway.

Materials and Methods: For hypoxic exposure, cells were incubated in a sealed hypoxic chamber flushed with a gas mixture of 94% N₂, 5% CO₂ and 1% O₂ in the presence of absence LMWF (25-100 μg/ml). In a xenograft mouse tumor model, the mice were administrated with vehicle (distilled H₂O) or LMWF (80-300 mg/kg/day, p.o.) for 30 days. Then, the pathological changes and target gene expression were examined.

Results and Conclusions: We demonstrated that LMWF significantly inhibits hypoxia-stimulated H₂O₂ formation, HIF-1α accumulation and transcriptional activity, vascular endothelial growth factor (VEGF) secretion, and the migration and invasion in hypoxic T24 cells. LMWF also downregulated hypoxia-activated phosphorylation of PI3K/AKT/mTOR/p70S6K/4EBP-1 signaling in T24 cells, which may provide a molecular mechanism accounting for inhibition of HIF-1α expression and VEGF secretion. Additionally, LMWF greatly attenuated the angiogenesis both in human umbilical vascular endothelial cells and in tumor accompanied by decrease of HIF-1α, and VEGF expression, and tumor growth.

Conclusion: Therefore, the antiangiogenic activity of LMWF in bladder cancer may be associated with suppressing HIF-1α/VEGF-regulated signaling pathway especially under hypoxia condition.

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Key Words: fucoidan; angiogenesis; hypoxia-inducible factor 1 alpha