（学位第３号様式）

学 位 論 文 要 旨

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題　目	The anti-inflammatory effects and molecular mechanisms of dietary flavonoids （フラボノイドの抗炎症作用及び分子機構に関する研究）

Flavonoids are widely included in vegetables and fruits, and reported to have various biological functions such as antioxidant and cancer preventive activities. Several lines of studies have shown that bioactivities of flavonoids depend on the antioxidant activity. However, flavonoids are known to be absorbed into the body in very small amount, it is hard to explain the multiple functions of flavonoids only with the antioxidant properties. In this study, I investigated the anti-inflammatory effects and molecular mechanisms of typical flavonoids in animal and cell models by targeting cellular signaling molecules.

First, I investigated the anti-inflammatory effects and molecular mechanisms of the representative flavonoids, quercetin (Q) and 8-prenyl quercetin (PQ), in animal and cell models. PQ attenuated mouse paw edema and serum IL-6 level, stronger than Q. Cellular and molecular data revealed that PQ had stronger inhibition on the productions of iNOS, COX-2, NO, PGE_2, and 12 kinds of cytokines, than Q. PQ and Q had no competitive binding to Toll-like receptor 4 (TLR4) with lipopolysaccharide (LPS), but directly targeted SEK1-JNK1/2 and MEK1-ERK1/2. Thus, PQ as a potential inhibitor, stronger than Q, revealed anti-inflammatory effect at least by targeting SEK1-JNK1/2 and MEK1-ERK1/2.

Next, I investigated the anti-inflammatory effects and molecular mechanisms of the polymeric flavonoid, theasinensin A (TSA), in animal and cell models. In the animal model, TSA suppressed the production of IL-12 (p70), TNF-α and MCP-1, and attenuated mouse paw edema induced by LPS. In the cell model, TSA reduced the levels of proinflammatory mediators including iNOS, NO, IL-12 (p70), TNF-α, and MCP-1 induced by LPS. Cellular signaling analysis revealed that TSA downregulated MEK-ERK signaling. Pull-down assay and affinity data revealed that TSA might directly bind to MEK-ERK for the inhibitory action.

In summary, these data demonstrated that flavonoids such as PQ, Q and TSA might directly bind to some protein kinases with different selectivity to inhibit inflammatory cellular signaling with attenuation of inflammatory mediator expressions and inflammation progression. These results from cell and mouse models provide a comprehensive data for understanding the anti-inflammatory effects and molecular mechanisms of dietary flavonoids.