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A Lower Molecular Weight(s) Isolated from *Agaricus blazei* Murill K (ABMK) as a Potent Multipotential Chemopreventive Agent(s) and the possible Molecular Mechanism(s) of Action.

アガリクス茸より抽出された低分子フラクションによる複合的がん化学予防及び分子メカニズムの可能性について

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アガリクス・ブラゼイ・ムリル（ABM：以下略してアガリクス茸）は日本では“ヒメマツタケ／カワリハラタケ”として幅広く知られており、特に生活習慣病に罹患している中高年層において非常に人気の高いサプリメントである。我々は協和アガリクス茸から抽出された分子量～500 の１SY１６フラクションを用いて齧歯動物の肺がん、結腸がん、乳がんに対する発がん抑制効果を評価した。1SY16 の発がん抑制効果は劇的であり、NNK/AOM/MNU といった発がん物質によって引き起こされるさまざまな分子イベントを有意に抑制した。DNA マイクロアレイを用いた分析においても１SY１６は NNK による多数の発がん遺伝子の発現阻止を含んだ複合的なメカニズムを示唆している。

Agaricus blazei Murill (ABM), widely known as “Himematsustake” in Japan, has been one of the most popular dietary supplements, especially among the aged-population with age-related disease. Chemopreventive effects of 1SY16, a low molecular fraction (～500D) isolated from ABMK was evaluated against carcinogen-induced pulmonary adenoma, ACF/colon tumors, and mammary tumors in rodents. Anticarcinogenic effects of 1SY16 were dramatic, and various relevant molecular events of NNK AOM and MNU-induced carcinogenesis were inhibited significantly. Possible mechanisms of 1SY16 actions were to counteract NNK-induced increase of up and down-regulated genes associated with inflammation, cell proliferation, apoptosis, and transformation, differentiation, activation of a variety of immune cells. These complex combinations of actions on relevant genes may be the basis of significantly reducing NNK-, AOM, and MNU-induced lung, colon, and mammary cancers, respectively.

The chemopreventive effects of 1SY16 (a low molecular weight isolated from kyowa’s *Agaricus blazei* Murill) was evaluated against three chemical carcinogen- induced experimental rodent models: NNK [4-(methylnitrosoamino)-1-(3- pyridyl)-1-butanone]-induced mouse pulmonary adenoma (PA), AOM (azoxy methane)- induced rat aberrant crypt foci (ACF) and colon carcinoma (CC), and MNU (methyl nitrosourea)-induced mammary tumors (MT) in rats.

The results showed that inhibition of PA, ACF/CC, and MT at their highest doses of 1SY16 was 88 (200mg/kg/7days), 85/35 (20mg/kg/10 days), and 45% (400mg/kg/40Days), respectively, and were statistically significant ($p<0.001$~0.05). Western blot analysis of cyclin D1, PCNA, and CDK4 in PA, and MT demonstrated that both cyclin D1 and PCNA in PA and MT were significantly inhibited by 95% each ($p<0.001$) in PA, and 42 and 32% ($p<0.05$) respectively in MT. In contrast, CDK4 gene was not inhibited either in PA or MT. In MT, a dose dependent inhibition of H-ras codon 12 transition mutation from GGA to GAA was completely inhibited after 30-days of 400mg 1SY16/kg b.w. treatment

A possible mechanism(s) of 1SY16 action against NNK-induced lung tumors was investigated using DNA microarray analysis. To understand the complex interactive pathways of up- or down regulated genes in the PA, the Ingenuity Pathway Analysis (v. 6.1) was used. A total of 40,000 genes was analyzed after the end of each month following 400mg 1SY16/kg. b.w. treatment for the first 10 days of each month. The results showed that possible mechanisms of 1SY16 actions significantly counteracted NNK-induced increase of genes involved in inflammation, cell proliferation, and other cancer related effects, while decreasing apoptosis, and immune cell function. In conclusion, 1SY16 isolated from ABMK may serve as a potentially useful cancer preventive agent against human cancers.