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NAG-1'S Role in Anti-tumorigenesis and Anti-obesity

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Nonsteroidal anti-inflammatory drug activated gene (NAG-1) is a newly-identified TGF- superfamily protein with anti-tumorigenic activity *in vitro* and *in vivo*. Although the transcriptional regulation of NAG-1 by a variety of signals, such as anti-inflammatory drugs and anti-tumorigenic compounds has been well established, the biological functions of NAG-1 have not been studied in detail. NAGis upregulated in human cancer cells by several NSAIDs, as well as by anti-tumorigenic dietary compounds, including resveratrol, genistein, diallyl disulfide, conjugated linoleic acid, green tea catechins, indole-3-carbinol, anti-diabetic drug PPAR ligands, 5F-203, retinoid 6-[3-(1-adamantyl)-4-hydroxyphenyl]-2-naphthalene carboxylic acid (AHPN), and 1,1-Bis(3′-indolyl)-1-(p-substituted phenyl)methanes.A very diverse number of chemicals with a wide range of chemical structures induce the expression of NAG-1, suggesting multiple mechanisms responsible for the increase in expression. Recently, we have developed NAG-1 transgenic mice and obtained NAG-1 knock-out mice, and thus are able to examine NAG-1's role in anti-tumorigenesis and other physiological functions *in vivo*. We have reported that NAG-1 transgenic mice are less sensitive to the carcinogenic compound that induces aberrant cryptic foci in the colon, and are less susceptible to tumor formation when crossed to a genetically modified animal model of intestinal tumorigenesis. In addition, we found that NAG-1 plays a pivotal role in urethane-induced lung tumorigenesis. During the course of studying NAG-1 transgenic mice, we have also found that they carry much lower body weight with reduced fat accumulation compared to their control siblings. Thus, NAG-1 can be induced by several anti-tumorigenic compounds, in that represents a novel target protein of anti-tumorigenesis and anti-obesity activity in vivo. Once the biological functions of NAG-1 are fully characterized, a secreted cytokine NAG-1 will be used for chemopreventive and/or therapeutic purposes in cancer and obesity in the future.

Keywords: AG-1, obesity, anti-tumorigenesis, transgenic Mice, chemoprevention

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The Role of RhoGDI2 in Gastric Cancer Metastasis

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Tumor invasion and metastasis are the critical steps in determining the aggressive phenotype of human cancers and the major causes of cancer deaths. Rho GTPases, including RhoA, Rac1 and cdc42 proteins, control a wide range of signalling pathways that regulate various biological processes. Aberrant signalling through these proteins, which is commonly found in human cancers, has been implicated in facilitating virtually all aspects of the malignant phenotype: increased tumor cell proliferation, promotion of angiogenesis, and acquisition of invasive and metastatic activities. The biological activities of Rho GTPases are mediated through a tightly regulated GDP/GTP cycle, which is stimulated by guanine nucleotide exchange factors (RhoGEFs) and terminated by GTPases-activating proteins (RhoGAPs). An additional level of regulation is provided by Rho GDP dissociation inhibitors (RhoGDIs). Three human RhoGDIs have been identified: RhoGDI1 (also known as RhoGDI or RhoGDI-α), RhoGDI2 (Ly-GDI or D4GDI or RhoGDI-β) and RhoGDI3 (RhoGDI-γ). RhoGDIs are endowed with dual functions in the cytosol where they form soluble complexes with prenylated GDP-bound Rho GTPases and at membrane where they monitor the delivery and extraction of Rho GTPases. In contrast to RhoGDI1 which is ubiquitous, RhoGDI2 is almost exclusively expressed in the hematopoietic lineages and has been called Ly-GDI or D4. RhoGDI2 has been usually known as a negative regulator of Rho GTPases and potential suppressor of tumor progression. In this study, we have shown that RhoGDI2 proteins are expressed only in human metastatic gastric and breast cancer cell lines and its mRNA expression level is correlated with gastric tumor stage. Forced expression of RhoGDI2 in cancer cells enhanced their invasiveness, while RhoGDI2 depletion by RNAi in RhoGDI2 expressing cancer cells reduced their invasiveness. Furthermore, tumor growth and lung metastasis *in vivo* was increased in RhoGDI2-overexpressing SNU-484 cells, compared to the control cells. RhoGDI2 specifically interacts with Rac1 and activates its activity. RhoGDI2 induces the expression of VEGF-C, one of the promoters of lymphangiogenesis and metastasis through activation of Rac1. Thus, we suggest that RhoGDI2 enhances motility and invasion of tumor cells and contributes to the promotion of metastasis in mice. The molecular mechanism of RhoGDI2, which was revealed by functional studies, provides insight into the process of tumor metastasis. Considering importance Rac1 on tumor progression and our results, RhoGDI2 may be a potent target for therapeutic intervention by interfacial inhibitors.

Key words: RhoGDI2, gastric cancer, metastasis, Rho GTPase, VEGF