様式３

論　文　内　容　の　要　旨

氏　名　（　小宮　優　）	
論文題名	The Rho guanine nucleotide exchange factor ARHGEF5 promotes tumor malignancy via epithelial-mesenchymal transition （グアニンヌクレオチド交換因子ARHGEF5は上皮間葉転換を介するがんの悪性化を促進する）

論文内容の要旨

Epithelial tumor cells often acquire malignant properties, such as invasion/metastasis and uncontrolled cell growth, by undergoing epithelial-mesenchymal transition (EMT). However, the mechanisms by which EMT contributes to malignant progression remain elusive. Here, we show that the Rho guanine nucleotide exchange factor (GEF) ARHGEF5 promotes tumor malignancy in a manner dependent on EMT status. We previously identified ARHGEF5, a member of the Dbl family of GEFs, as a multifunctional mediator of Src-induced cell invasion and tumor growth. In the present study, ARHGEF5 was upregulated during TGF-β-induced EMT in human epithelial MCF10A cells, and promoted cell migration by activating the Rho-ROCK pathway. ARHGEF5 was necessary for the invasive and in vivo metastatic activity of human colorectal cancer HCT116 cells. These findings underscore the crucial role of ARHGEF5 in cell migration and invasion/metastasis. An in vivo tumorigenesis assay revealed that ARHGEF5 had the potential to promote tumor growth via the PI3K pathway. However, ARHGEF5 was not required for tumor growth in epithelial-like human colorectal cancer HCT116 and HT29 cells, whereas the growth of mesenchymal-like SW480 and SW620 cells depended on ARHGEF5. Induction of EMT by TNF-α or Slug in HCT116 cells resulted in the dependence of tumor growth on ARHGEF5. In these mesenchymal-like cells, Akt was activated via ARHGEF5 and its activity was required for tumor growth. Aanalysis of a transcriptome dataset revealed that the combination of ARHGEF5 upregulation and E-cadherin downregulation or Snail upregulation was significantly correlated with poor prognosis in patients with colorectal cancers. Taken together, our findings suggest that EMT-induced ARHGEF5 activation contributes to the progression of tumor malignancy. ARHGEF5 may serve as a potential therapeutic target in a subset of malignant tumors that have undergone EMT.

様式 7

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

小宮氏は、がんの悪性化（転移能や浸潤能の獲得）機構の一つとされる上皮間葉転換（EMT）の分子メカニズムの解明を目指し、Rho guanine nucleotide exchange factor (GEF)の一つであるARHGEF5に着目し、様々な角度からその機能解析を行った。その結果、ARHGEF5がEMTに伴って活性化し、Srcキナーゼと協調してがん細胞の浸潤転移に重要な役割を担うこと、また、PI3K-AKT経路を活性化することによって、AKT依存的に腫瘍形成を促進することを見出した。さらに、ARHGEF5の高発現がEMTに依存してヒト大腸がんの予後と有意に相関することも突き止めた。これらの新たな発見は、がんの悪性化機構を解明する上できわめて重要な知見であり、創薬への応用も期待されると判断される。よって、本論文は博士（理学）の学位論文として十分価値あるものと認める。