

## News Release

### Title

Connective tissue growth factor and  $\beta$ -catenin constitute an autocrine loop for activation in rat sarcomatoid mesothelioma

### Key Points

- **Connective tissue growth factor (CTGF) expression was significantly increased in sarcomatoid mesothelioma (SM) compared to epithelioid mesothelioma (EM), which induced more invasive and malignant features in the asbestos-induced rat mesothelioma.**
- **CTGF stimulated Wnt/ $\beta$ -catenin-TCF pathway through its receptor on plasma membrane, followed by CTGF production and secretion. These mechanisms constituted a positive feedback loop.**
- **CTGF is a serum biomarker for the diagnosis of MM, especially sarcomatoid type, and is a good candidate for molecular target therapy.**

### Summary

Shinya Toyokuni (Professor, Department of Pathology and Biological Responses), Li Jiang (Assistant professor, Department of Pathology and Biological Responses) and his team from Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, MD, PhD) found that connective tissue growth factor (CTGF) is significantly highly expressed in sarcomatoid mesothelioma (SM) than epithelioid mesothelioma (EM), based on a rat asbestos-induced mesothelioma model. CTGF induced the activation of Wnt/ $\beta$ -catenin pathway, generating an autocrine loop through its secretion and its receptor on the plasma membrane. Therefore, CTGF can function as a serum diagnostic and prognostic marker for SM, and is a good candidate for molecular target therapy. This work was published online in *The Journal of Pathology* on May 19, 2014.

### Research Background

Asbestos was used worldwide in huge quantities in the last century. However, because of its unexpected carcinogenicity to mesothelial cells with an extremely long incubation period, many countries face this long-lasting social problem. Mesothelioma is often diagnosed in an advanced stage, for which no effective therapeutic protocols are yet established. SM presents much poorer

prognosis than EM. We previously established a rat model of peritoneal mesothelioma with commercially used asbestos and noticed a higher incidence of SM in comparison to human cases. Thus, this model allowed efficient studies on SM to identify potential genes responsible for its aggressiveness.

### **Research Results**

Based on the results of transcriptome analysis, we singled out a candidate gene, connective tissue growth factor (CTGF), whose expression was most significantly increased in SM compared with EM and was under a positive feedback loop in association with  $\beta$ -catenin. Of note, even EM showed a significantly higher expression in comparison to normal mesothelial cells. We further found that CTGF was secreted from mesothelioma and can function as a serum diagnostic and prognostic marker for rat mesothelioma, especially for SM. In addition, CTGF induced epithelial-mesenchymal transition (EMT)-like morphological alterations in MM.

### **Research Summary and Future Perspective**

CTGF is a novel and significant serum biomarker of mesothelioma, especially for SM, both for early diagnosis and prognosis in the rat model. These data link SM and CTGF overexpression through the LRP6/GSK3 $\beta$ / $\beta$ -catenin/TCF/CTGF autocrine axis and suggest CTGF as a serum marker and a molecular therapeutic target.

Li Jiang, Yoriko Yamashita, Shan-Hwu Chew, Shinya Akatsuka, Shun Ukai, Shenqi Wang, Hirotaka Nagai, Yasumasa Okazaki, Takashi Takahashi and Shinya Toyokuni. Connective tissue growth factor and  $\beta$ -catenin constitute an autocrine loop for activation in rat sarcomatoid mesothelioma.

*The Journal of Pathology* (May 19, 2014) .

### **Japanese ver.**

[http://www.med.nagoya-u.ac.jp/medical/dbps\\_data/material/nu\\_medical/res/topix/2014/CTGF\\_20140519jp.pdf](http://www.med.nagoya-u.ac.jp/medical/dbps_data/material/nu_medical/res/topix/2014/CTGF_20140519jp.pdf)

## Epithelial-mesenchymal transition

