N-WASP, a colorectal cancer suppressor?

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Colorectal cancer is one of the leading causes of cancer mortality in the world. However, this disease is highly preventable, even curable, when detected early and treated appropriately. Diagnosis of colorectal cancer usually relies on the biopsy that is collected by sigmoidoscopy and colonoscopy and analyzed by using histological techniques (1). With respect to the treatment, surgery is still the most preferred approach, providing that the patient's condition permits. Doctors need to choose a relatively proper surgery strategy, usually referring to the timely pathological report of rapid frozen tissues collected during operation (2). Therefore seeking sensitive and specific indicators or biomarkers, which may provide assistance to both diagnosis and therapy of colorectal cancer, has been one of the major orientations for scientists' endeavor in this area.

Wiskott-Aldrich syndrome (WAS) is an inherited, X-linked and recessive disease which is caused by mutations in the WAS gene. These mutations may also increase genomic instability (3), leading to the occurrence of diseases including cancers (e.g., lymphoma). However, it has been argued whether the WAS proteins (WASPs) themselves serve as cancer suppressors or enhancers (4).

Martin *et al*. have recently examined whether the molecule, neural Wiskott-Aldrich syndrome protein (N-WASP), is associated with the disease progress and clinical outcome of human colorectal cancer (5). For this purpose, N-WASP expression in human colon tissues was examined by immunohistochemical staining and real-time quantitative PCR (RT-PCR). The correlation between N-WASP expression and clinical characteristics in colon cancer patients was analyzed. Consistent with their previous study performed in human breast cancer, expression of N-WASP in human colon tumor tissues was lower than that in normal, an observation that was closely related to tumor invasion. They also found that the levels of N-WASP in tissues with tumor-positive nodes and muscular invasion were significantly lower than those with node-negative and non-inavsive tumors. Their data also demonstrated that loss of N-WASP led to a poor clinical outcome. These data indicated that N-WASP expression is inversely correlated with the disease progression and clinical outcome of colon cancer patients.

The authors further demonstrated that over-expression of N-WASP in HRT18 human colon cancer cells significantly inhibit the cancer cell growth, migration and invasion; depletion of N-WASP promoted the migration and invasion, but had little effect on the cell growth. Although more cell lines should be examined, the results suggest that N-WASP is a potential tumor suppressor. These findings are interesting as they raise the possibility that N-WASP might serve as a potential biomarker for diagnosis and prognosis of human colorectal cancer. Since N-WASP can be ubiquitinated and degraded (6), the pathway that controls N-WASP ubiquitination could be a potential therapeutic target for colorectal cancer.

Nevertheless, the inverse correlation between N-WASP expression and tumor progression is not supported by the analysis on tumor staging. The authors demonstrated that N-WASP greatly expressed in tumors at stage TNM-2 or Dukes-B but rarely at the early stage, namely stage TNM-1or Dukes-A. Yanagawa *et al*. also showed that tissues collected from the metastatic sites in liver exhibited higher N-WASP level than the primary colon tumors (7). These results point to the role of N-WASP as a metastasis enhancer. This seems to be supported by *in vitro* cell function studies using other cancer cell types. For example, activated N-WASP usually appears at the leading

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edge of lamellipodium extensions as well as in invadopodia in melanoma and breast cancer cells (8,9); activation of N-WASP promotes invadopodium formation, cell motility and invasion in MDA-MB-231 cells (10). On the other hand, Martin *et al.* showed that knocking down N-WASP in the HRT18 human colon cancer cells significantly enhanced cell motility and cell invasion in response to growth factor. Thus, the role of N-WASP in colon cancer metastasis is not conclusive and further studies using larger sample size and more cell lines may resolve the inconsistence. It is also possible that N-WASP ubiquitination instead of the expression levels of N-WASP regulates cancer metastasis.

In summary, N-WASP protein could be a suppressor as well as a potential biomarker for diagnosis and prognosis of human colorectal cancer. However, detailed relationship between N-WASP expression and colon cancer progression and metastasis and mechanisms by which N-WASP suppresses colorectal cancers require further investigation.

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