Suppression of Metastasis—A New Function for Known Proteins

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In this issue of the Journal, Chang et al. (1) report the identification of an unanticipated function for connective tissue growth factor (CTGF) in the regulation of aspects of lung cancer metastasis. Their data add to a growing body of literature identifying new functions of known proteins in the regulation of metastatic growth. The functional identification of metastasis suppressor proteins requires appropriately designed in vitro, in vivo, and clinical correlative studies to assess the role of the candidate protein in the metastatic process (2). To this end, the authors present three lines of evidence to support their assertion that CTGF functions as a metastasis suppressor in lung cancer. First, ectopic expression of CTGF in adenocarcinoma cell lines that had low to undetectable levels of endogenous CTGF protein decreased Matrigel invasion in vitro. Second, complementary studies showed that ectopic expression of CTGF suppressed the ability of adenocarcinoma cells to colonize the lung in experimental metastasis assays. Finally, clinical studies showed that reduced expression of CTGF was associated with the risk of more advanced-stage disease, lymph node metastases, and shorter survival.

How can we incorporate the findings of CTGF activity by Chang et al. into our current understanding of metastasis? Metastatic competence requires a complex set of cellular functions that are associated with a cadre of molecular and cellular changes (2). The ability to invade through a basement membrane is a hallmark of metastatic cells. Traditionally, metastasis researchers have used invasion through Matrigel to evaluate the invasive potential of tumorigenic and metastatic cell lines. They based this approach on the observation that a cell’s in vitro invasive ability is often associated with its ability to form metastases in vivo (3). Chang et al. present compelling data showing that ectopic expression of CTGF suppresses the in vivo invasive ability of two metastatic adenocarcinoma cell lines.

For more than two decades, researchers believed that escape of a cell from the primary tumor was the rate-limiting event that determined metastasis formation (4). Recently, multiple lines of evidence have shown that disseminated cancer cells are subject to post-extravasation growth controls (5,6). These studies show unequivocally that invasive tumor cells can leave a primary tumor but often fail to proliferate at an ectopic site (2,7). Thus, cellular proliferation at the metastatic site, a process termed “metastatic colonization,” must be considered a potential rate-limiting step of metastasis. In their study, Chang et al. have shown that ectopic expression of CTGF suppressed the ability of non–small-cell lung cancer cells to colonize a target organ—the lung.

How does CTGF function to suppress metastasis? Metastasis suppressor genes are operationally defined as genes that encode proteins that suppress the formation of overt metastases but exert no measurable effect on in vitro or in vivo proliferation (2). Metastasis is a dynamic process that requires cells to sequentially invade local tissues and disseminate from the primary tumor, lodge in and extravasate from the microvasculature at a secondary site, and finally form microscopic colonies that can give rise to clinical metastases (8). Proteins encoded by metastasis suppressor genes can block any step in this process, the net result being suppression of overt metastases (5). Data from Chang et al. (1) suggest that CTGF interferes with invasion and affects metastatic colonization. These findings are of particular interest because there is currently a paucity of understanding regarding the specific genes and signaling molecules that regulate lung cancer metastases.

Chang et al. found an intriguing link between the ectopic expression of CTGF and increased expression of the collapsin response mediator protein 1 (CRMP-1). In a previous study (9), the authors have shown that CRMP-1, an intracellular phosphoprotein, is involved in cell migration and invasion. The authors postulate that CTGF causes an increased expression of CRMP-1 and that CTGF suppresses metastasis through a CRMP-1–dependent mechanism. It is anticipated that demonstration of such a mechanism will improve our understanding of how these two proteins function to suppress invasion and metastasis. It will also be important to integrate CTGF and CRMP-1 function into the context of other known metastasis suppressors, including both novel (NM23, BRMS1, KiSS1, and KA11) and known (MKK4 and RKIP) metastasis suppressors (10,11). Biochemical interactions between metastasis suppressor proteins such as MKK4, NM23, and RKIP are being identified, and it is anticipated that metastasis suppressor cascades will emerge from these studies. It will be interesting to see whether molecules such as CTGF and CRMP-1 have independent functions or fit into these prospective networks.

What is the potential clinical value of CTGF, CRMP-1, and the known metastasis suppressor proteins? The identification of specific signaling pathways that regulate metastatic growth is an important advance, yet there are substantial roadblocks to successful incorporation of this knowledge into clinical practice. First, the individual metastasis suppressor protein must be considered in terms of the pathway in which it participates. Simply turning a single gene (protein) “on” or “off” in a signal transduction pathway will inevitably have broader effects than intended, because each pathway may affect, positively or negatively, the regulation of many as yet undocumented processes. The context-specific nature of signal transduction may limit our ability to generalize the effects of modulating a specific pathway.
to other model systems or tissue types. For example, although the MKK4-mediated activation of the JNK/p38 pathway has an established association with metastasis suppression in prostate and ovarian carcinomas (12,13), activation of this same pathway may have a role in the malignant transformation of small-cell lung carcinomas (14). Similarly, increased CTGF expression is associated with poor disease-free survival in breast, pancreatic, and skin cancers but can potentially function to suppress lung cancer metastasis (1,15–17). Thus, it is likely that the effect of a specific signaling pathway may have to be determined on a case-by-case basis. The importance of these caveats to the successful utilization of metastasis suppressor function in the clinical setting cannot be overstated. The context dependency of both the biologic and biochemical regulation of metastatic growth necessitates the identification of both general and specific metastasis-regulating proteins. Chang et al. have provided an intriguing piece to the understanding of the puzzle of lung cancer metastasis.

REFERENCES


NOTES

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