The matricellular protein CYR61 promotes lung metastasis of breast cancer cells through facilitating transmigration and anoikis resistance during extravasation

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Cysteine-rich 61 (CYR61) belongs to the CCN (CYR61/CTGF/NOV) family of matricellular proteins, and regulates cell proliferation, migration, apoptosis through binding with different integrin receptors or heparin sulfate proteoglycans. Recently, the significant contribution of microenvironment matricellular proteins during cancer progression has been gradually unveiled. However, how these proteins involve in the multistep formation of life-threatening metastases still needs to be further elucidated.

In this study, we showed that, by knocking down CYR61, breast cancer cells growing in pre-irradiated mammary fat pads formed less lung metastasis. The promoting effect of CYR61 during natural course of cancer metastasis was further confirmed using the conventional orthotopic xenograft model without irradiation and the tail-vein xenograft model. At the time-point of 24 hours after tail-vein injection, there were already less cancer cells retained in the lung parenchyma of mice injected with CYR61-knocking down (KD) cells. In addition, delayed induction of CYR61 shRNA 24 hours after tail-vein injection compromised the decreasing effect of knocking down CYR61 on lung metastasis formation, indicating that CYR61 promotes metastasis formation mainly through facilitating extravasation instead of the following step of colonization in lung. Besides the well-known function of CYR61 on enhancing migratory ability, we showed here for the first time that CYR61 also supports cell survival under anoikis. By using chemical inhibitors and shRNA, we demonstrated that the CYR61-maintained anoikis resistance was independent of activation of ERK1/2 pathway, but partially mediated by the activation of AMPK pathway. Overall, our data provide the first evidence that CYR61 expression promotes lung metastasis formation of breast cancer cells through facilitating migration and supporting anoikis resistance during extravasation. These results indicate the potential of CYR61 to serve as a predictive marker for the risk of distant metastasis spreading and as a therapeutic target to develop in the future.