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#302 CCR5 and CCRL2 accommodating responses to CCL5 induces directional cancer cells migration and organ specific metastasis. Hui-Wen Chang, Hui-Ju Li, Chia-Ling Hsieh, Shian-Ying Sung. China Medical Univ., Taichung, Taiwan.

Environmental factors have profoundly influence on cancer cell directional migration and metastasis. Previously, we have showed the increasing of CCL5 in tumor associated stromal cells and in patient sera with cancer progression. To verify the role of CCL5 in organ specific cancer metastasis, cellular and molecular studies of cancer migratory activities induced by CCL5 was conducted. Cell tracking assays indicated CCL5 strongly involved in the directional migration. Furthermore, quantitative PCR indicated significant increasing of CCRL2 in AIPC that can be confirmed by western blot and flow cytometry analyses. Knockdown of CCRL2 declined 75% of migration activities induced by CCL5, suggests CCRL2 involve in CCL5 induce cancer metastasis. To verify the interaction between CCRL2 and CCL5, biotinylated CCL5 binding assay demonstrated CCL5 independently binding to both CCR5 and CCRL2. Knockdown of CCRL2 decreased prostate cancer directional migration induced by CCL5. However, shCCRL2 did not decrease CCR5 downstream signal activities, suggests differential biological activities of CCR5 and CCRL2 induced by CCL5. Reduction of CCRL2 expression decreased CCR5 polarization into the leading edge of migration front after treating with CCL5, indicated CCRL2 assisting CCR5 polarization. Knockdown of CCRL2 significantly decreased CDC42 GTP and GDP turn-over rate. Immunohistochemical studies of CCRL2 expression in prostate cancer patient samples revealed increasing of CCRL2 expression in malignant prostate cancer locus, whereas no CCRL2 can be detected in the benign region of same patient. T2 stage prostate cancer showed lower of CCRL2 expression compared to T4 stage. In addition, increased of CCRL2 expression can be detected at invasion front. By contrast, bone metastasis tissue showed no CCRL2 expression. This suggests CCRL2 transiently increasing during initial metastasis once sensing environmental cues and decreased the expression after settled at the distant organs. To determine the role of CCRL2 in initiation of metastasis, cell sorting of $CCRL2^{lo}$ and $CCRL2^{hi}$ into two groups and cultured for additional two weeks showed ≥90% of $CCRL2^{hi}$ converted back to $CCRL2^{lo}$ with only ≤10% remain in high-expression group. Cell tracking assay demonstrated strong directory migration activities exists in cancer cells with $CCRL2^{hi}$ compared to $CCRL2^{lo}$. These data suggests transient increasing expression of CCRL2 play a central role in cancer directional cell migration induced by CCL5. Our data indicating organ specific metastasis might through the cooperation of multiple factors that determine cancer initial migration and invasion, and metastasis activities. (This work was supported by a grant NHRI EX-100-9902BI, Taiwan to SY Sung).

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