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Molecular and Cellular Biology of Cancer; Cancer Stem Cell

Research Interests

The patients of cancer represent a huge public health burden worldwide. It currently ranks as the first leading cause of death in Taiwan. Cancer formation is a multi-step process during which genetic and epigenetic events determine the transition from a normal to a malignant cellular state. In the past 10-20 years, extensive effort has been made not only to figure out the molecular mechanisms underlying progression to malignancy but also to identify possible molecular targets for therapy. However, the complex molecular interplay leading to cancer is very poorly understood. Common to most tumors, several regulatory mechanisms are altered during multistage tumor formation and progression, most importantly, the control of proliferation, the balance between cell survival and programmed cell death (apoptosis), the communication with neighbouring cells and the extracellular matrix (ECM), the induction of tumor neovascularization (angiogenesis) and, finally, tumor cell migration, invasion and metastatic dissemination.

The type I transmembrane glycoprotein CD44, long-known as a cell-adhesion molecule, is frequently overexpressed in its larger variant isoforms in human cancers. The CD44v6 has been identified as a prognostic marker in many cancers. In addition, CD44 has recently been identified as a signature for cancer stem cells (CSCs) isolated from various tissues. This sub-population of cancer cells are relatively resistant to therapy and may possibly be responsible for disease recurrence. Therefore, CD44-expressing cells may represent important mediator for cancer progression. However the mechanisms underlying CD44's action remains largely unknown. We have previously shown that interaction of CD44v and its physiological ligand osteopontin (OPN), both being frequently overexpressed in gastric cancer, confers cells an increased matrix-derived survival through the establishment of CD44-Src-Integrin signaling axis in lipid rafts. Recently, we found that ligation of CD44 promotes its internalization through endocytosis, and the internalized receptor is translocated to nucleus and regulates gene expression. We found that wild-type CD44, but not the nuclear localization-defective CD44(NLS) mutant interacts with transcriptional modules and promotes cell proliferation through STAT3-mediated

transactivation. In parallel, we also showed that the expression of wild-type CD44 but not CD44(NLS) supports cancer cell growth in non-adherent suspension as spheroid culture, with concomitant induction of epithelial-mesenchymal transition (EMT) markers. Based on these findings, we propose that CD44, once translocated into nucleus, may induce transcription reprogramming which in turn gives cells a competitive edge for growth, survival and invasiveness thus facilitate tumor progression. CD44-mediated transcription modulation may play important roles in cancer and cancer stem cell.

Recent Publications

1. **Lee J. L.**, Wang M. J., Lai H. M., and Chen J. Y. (2009) Acetylation and activation of STAT3 mediated by nuclear translocation of CD44. J. Cell Biol.; (in press) **(SCI, Impact Factor: 12.023)**
2. **Lee J. L.**, Wang M. J., Sudhir P. R., and Chen J. Y. (2008) CD44 Engagement Promotes Matrix-derived Survival through CD44-SRC-integrin Axis in Lipid Rafts. Mol. Cell Biol. 28: 5710-5723. **(SCI, Impact Factor: 7.822)**
3. **Lee J. L.**, Wang M. J., Sudhir P. R., Chen G. D., Chi C.W., and Chen J. Y. (2007) Osteopontin promotes integrin activation through outside-in and inside-out mechanisms: OPN-$CD44_V$ interaction enhances survival in gastrointestinal cancer cells. Cancer Res. 67: 2089-2097. **(SCI, Impact Factor: 7.616)**
4. **Lee, J. L.**, Chang, C. J., Chueh, L. L., and Lin, C. T. (2006) Secreted Frizzled Related Protein 2 (sFRP2) Decreases Susceptibility to UV-Induced Apoptosis in Primary Culture of Canine Mammary Gland Tumors by NF-kappaB Activation or JNK Suppression. Breast Cancer Res Treat. 100: 49-58. **(SCI, Impact Factor: 4.643)**
5. **Lee, J.L.**, Chang, C. J., Wu, S. Y., Sargan, D. R., and Lin, C. T. (2004) Secreted Frizzled-related protein 2 (SFRP2) is highly expressed in canine mammary gland tumors but not in normal mammary glands. Breast Cancer Res. Treat. 84: 139-149. **(SCI, Impact Factor: 4.643)**
6. **Lee, J. L.**, Lin, C. T., Chueh, L. L., and Chang, C. J. (2004) Autocrine/paracrine SFRP2 induces cellular resistance to apoptosis: a possible mechanism of mammary tumorigenesis. J. Biol. Chem. 279: 14602-14609. **(SCI, Impact Factor: 6.355)**
7. **Lee, J. L.**, Chang, C. J., Chueh, L. L., and Lin, C. T. (2003) Expression of secreted frizzled-related protein 2 in a primary canine mammary tumor cell line: a candidate tumor marker for mammary tumor cells. In. Vitro. Cell Dev.

Biol. Anim. 39: 221-227. **(SCI, Impact Factor: 0.718)**

8. Lin, C.T., and **Lee J. L.** (2002) Clinical and laboratory diagnosis of ulcerative keratitis in dogs and cats. J. Chin. Soc.Vet. Sci. 28(2): 106-112.
9. Yeh, L. H., **Lee, J. L.**, Chen, C. M. and Chang, P. H. (1999) Case report: Arare case of canine inflammatory mammary carcinoma. J. Chin. Soc. Anim. Sci. 25: 309-315.
10. Lin, C. T., Lin, Y. W., **Lee, J. L.** (1999) The use of conjunctival flap to repair deep corneal ulcer and descemetocele in dogs and cats. J. Chin. Soc. Anim. Sci. 25 (supplement): 98.
11. Lin, C. T., **Lee, J. L.**, Lin, Y. W. 1999.The clinical and laboratory profiles of canine and feline ulcerative keratitis at the NTUVH. J. Chin. Soc. Anim. Sci. 25 (supplement): 95.