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Ph.D., Institute of Veterinary Medicine, National Taiwan University, 2004.
Molecular and Cellular Biology of Cancer; Cancer Stem Cell

RESEARCH INTEREST

The Cancer Stem Cell (CSC) Hypothesis

The major component of the CSC hypothesis is that tumors contain and are ‘‘driven’’ by cellular components that display stem cell properties. CSCs represent malignant cell subsets in hierarchically organized tumors, which are selectively capable of tumor initiation and self-renewal and give rise to bulk populations of non-tumorigenic cancer cell progeny through differentiation. Robust evidence for the existence of prospectively identifiable CSCs among cancer bulk populations has been generated using marker-specific genetic lineage tracking of molecularly defined cancer subpopulations in competitive tumor development models. Moreover, novel mechanisms and relationships have been discovered that link CSCs to cancer therapeutic resistance and clinical tumor progression. Importantly, proof-of-principle for the potential therapeutic utility of the CSC concept has recently been provided by demonstrating that selective killing of CSC through a prospective molecular marker can inhibit tumor growth. CSC theory has prompted some investigators to re-examine more established views of tumor initiation, cancer progression, and therapeutic resistance, with a view to develop novel CSC-directed therapeutics that might synergize with currently available treatments predominantly directed at cancer bulk populations, and that might hence serve to improve clinical cancer therapy.

Paracrine Factors and Niche Structure in Cancer Stem Cell

Stem cells reside in a special microenvironment called the niche. Stem cells interact with the niche via adhesion molecules and exchange molecular signals that maintain the specific features of stem cells. Canonical Wnt signaling has been implicated in maintaining regulation of the stem cell microenvironment. As a key paracrine secreted factor, it controls stem cell fate by suppressing differentiation and promoting self-renewal as seen in skin, intestine, breast, and other tissues including lung. Activation of Wnt signaling is further controlled by different antagonists, including Wnt inhibitory factor 1 (WIF1), Cerberus, Sclerostin, and members of the Dickkopf and secreted Frizzled-related protein (SFRP) families. A better understanding of the nature of stem cells and their niches is expected to provide an alternative approach to the treatment of various serious diseases, including cancer, in clinical practice. The studies in my lab mark a step towards realizing these hopes, and provide further insight into the CSC niche of human cancers. We have previously shown that CD44, once engaged, is internalized and translocated to the nucleus, where it binds to various promoters, including that of *SFRPs*, leading to cell fate change through transcriptional reprogramming. We provide

concrete experimental rationale for using SFRP family as markers to identify CSCs and further figure out how and why SFRP family are regarded as CSC markers. We dissect the SFRPs-elicited molecular pathways and mechanisms, such as those involved in self-renewal, migration (the epithelial-mesenchymal transition) and drug-resistance, are shared by CSCs and their normal counterparts. In addition, we show the therapeutic promise of CSC-directed treatment strategies, which could facilitate eradication of tumors currently resistant to systemic therapy and thus potentially result in patient cures.

Stem Cell Characteristics Relating to Dormancy and Metastasis

The majority of cancer deaths occur as a result of metastatic disease rather than from the effects of the primary tumor. Furthermore, elucidation of the mechanisms regulating clinical tumor dormancy and those involved in disease relapse remain two of the most important and provocative challenges in cancer biology. The inefficiency of the metastatic process, the inherently heterogeneous nature of solid tumors, and the influence of the tumor microenvironment dictate that only a small subset of cells (potentially cancer stem cells) can successfully navigate the metastatic cascade and eventually re-initiate tumor growth to form life-threatening metastases. Moreover, experimental models of tumor dormancy have demonstrated that these influences can also play significant roles in maintaining tumor dormancy or triggering proliferation and disease progression. In cancer patients, it is believed that metastatic cancer cells may remain dormant for decades until some unknown mechanism triggers them to proliferate and progress to clinically relevant metastases. However, increasing support for the CSC hypothesis alternatively suggests that the dormant disseminated cells in this patient population may actually arise from “non-tumorigenic” cells, and it is only when CSCs disseminate (and/or respond to a favorable stem cell microenvironment) that they subsequently self-renew and patients relapse with metastatic disease. Understanding the functional and mechanistic role that CSCs may play in determining tumor dormancy and metastatic potential could therefore have significant implications for the way we currently study, diagnose, and treat human cancer.

Recent Publications (2007-2012)

1. Su, Y. J., Lai, H. M., Chang, Y. W., Chen, G. Y. and **Lee, J. L.*** (2011). Direct reprogramming of stem cell properties in colon cancer cells by CD44. EMBO Journal **30**(15): 3186-3199. (*corresponding author).
2. **Lee, J. L.**, Wang, M. J. and Chen, J. Y. (2009). Acetylation and activation of STAT3 mediated by nuclear translocation of CD44. Journal of Cell Biology **185**(6): 949-957.
3. **Lee, J. L.**, Wang, M. J., Sudhir, P. R. and Chen, J. Y. (2008). CD44 engagement promotes matrix-derived survival through the CD44-Src-integrin axis in lipid rafts. Molecular and Cellular Biology **28**(18): 5710-5723.

4. **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 Research **67**(5): 2089-2097.

Awards

2008	Outstanding Research Award, Juei-Low Sung Foundation, Taiwan.
2004	The Award of Academic Research Thesis in Doctor, College of Bio-resourres and Agriculture, National Taiwan University, Taiwan.
2000-2002	Outstanding Research Award, Graduate Institute of Veterinary Medicine, National Taiwan University, Taiwan.
2000	Outstanding Research Award, The Society of Chinese Veterinary Science, Taiwan.
1997-1999	Tuition Fee Scholarship, National Taiwan University, Taiwan.