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**Professor**

**Ph.D., Institute of Veterinary Medicine, National Taiwan University, 2004.**

**Molecular and Cellular Biology of Cancer; Cancer Stem Cell**

**Research Interests**

**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 (2016-2021)***

* 期刊論文
1. Lin W. H., Chang Y. W., Hong M. X., Hsu T. C., Lee K. C., Lin C., Lee J. L. \* (2021). STAT3 phosphorylation at Ser727 and Tyr705 differentially regulates the EMT–MET switch and cancer metastasis. Oncogene 40:791-805. (SCI, IF = 9.867). 本人為通訊作者.
2. Chen W. J., Lai Y. J., Lee J. L., Wu S. T.g, Hsu Y. J. (2020). CREB/ATF3 signaling mediates indoxyl sulfate-induced vascular smooth muscle cell proliferation and neointimal formation in uremia. Atherosclerosis 315: 43-54. (SCI, IF = 5.162).
3. Liang C. J., Wang Z. W., Chang Y. W., Lee K. C., Lin W. H., Lee J. L. \* (2019). SFRPs are biphasic modulators of Wnt-signaling-elicited cancer stem cell properties beyond extracellular control. Cell Reports 28: 1511-1525. (SCI, IF = 9.423). 本人為通訊作者.
4. Chen W. J., Chang S. H., Chan Y. H., Lee J .L., Lai Y. J., Chang G .J., Tsai F. C., Yeh Y. H. (2019). Tachycardia-induced CD44/NOX4 signaling is involved in the development of atrial remodeling. Journal of Molecular and Cellular Cardiology 135: 67-78. (SCI, IF = 5.000)
5. Chang S. H., Yeh Y. H., Lee J. L., Hsu Y. J., Kuo C. T. and Chen W. J. (2017). Transforming growth factor-β-mediated CD44/STAT3 signaling contributes to the development of atrial fibrosis and fibrillation. Basic research in cardiology 112:58. (SCI, IF = 17.165).
6. Chang Y. W., Su Y. J., Hsiao M., Wei K. C., Lin W. H., Liang C. L., Chen S. C., and Lee, J. L.\* (2015). Diverse targets of β-catenin during the epithelial–mesenchymal transition define cancer stem cells and predict disease relapse. Cancer Research 75:3398-3410. (SCI, IF = 12.701). 本人為通訊作者.
7. Su Y. J., Chang Y. W., Lin W. H., Liang C. L., Lee J. L.\* (2015). An aberrant nuclear localization of E-cadherin is a potent inhibitor of Wnt/β-catenin-elicited promotion of the cancer stem cell phenotype. Oncogenesis 4: e157. (SCI, IF = 7.485). 本人為通訊作者.
* 研討會論文
1. Lin W. H., Chang Y. W., and Lee J. L\* (2019, Jan). CD133/RalA/PAR6/The Exocyst Complex Upregulates Tumor Exosome Integrins to Determine Organotropic Metastasis. 2019 Asian Conference on Engineering and Natural Sciences, Sapporo, Japan. 本人為通訊作者.
2. Chang Y. W., Lin W. H., and Lee J. L\* (2018, March). CD133/RalA/PAR6/The Exocyst Complex Upregulates Tumor Exosome Integrins to Determine Organotropic Metastasis. 2018 Asia-Pacific Conference on Life Science and Biological Engineering, Kyoto, Japan. 本人為通訊作者.
3. Chang Y. W., Lin W. H., Liang C. J., Su Y. J., Wang Z. W., and Lee J. L.\* (2017, Jan). Bone Marrow-Derived Mesenchymal Stem Cells Contribute to the Cancer Stem Cell Niche and Promote Tumor Metastasis. 2017 Asian Conference on Engineering and Natural Sciences, Sapporo, Japan. 本人為通訊作者.
4. Su Y. J., Lin W. H., Liang C. J., Chang Y. W., Wei K. C., and Lee J. L.\* (2016, Oct). Molecularly Therapeutic Strategies Targeting the CD133-Integrin Interaction in Inhibiting Cancer Stem Cell Formation and Preventing Tumor Metastasis. 2016 International Conferences: Academic & Multidisciplinary, Osaka, Japan. 本人為通訊作者.
5. Chang Y. W., Su Y. J., Hsiao M., Wei K. C., Lin W. H., Liang C. L., Chen S. C., and Lee J. L.\* (2015, May). Epithelial-Mesenchymal Transition Acts as a Molecular Switch for Wnt/β-catenin-Elicited Reprogramming to a Cancer Stem Cell Phenotype. Biology of Cancer: Microenvironment, Metastasis and Therapeutics, Cold Spring Harbor Laboratory, New York, USA. 本人為通訊作者.
6. Liang C. J., Wang Z. W., Lin W. H., and Lee J. L.\* (2015, May). Secreted Frizzled-related Proteins Define the Cancer Stem Cell Population within a Wnt-dependent Stem Cell Niche. Biology of Cancer: Microenvironment, Metastasis and Therapeutics, Cold Spring Harbor Laboratory, New York, USA. 本人為通訊作者.
7. Chang Y. W., Su Y. J., Hsiao M., Wei K. C., Lin W. H., Liang C. L., Chen S. C., and Lee J. L.\* (2015, May). Diverse Targets of the Transcription Cofactor β-catenin During Epithelial-Mesenchymal Transition Contribute to Reprogramming of Stem Cell Properties. International Congress on Chemical, Biological and Environmental Sciences, Kyoto, Japan. 本人為通訊作者.

***Honor***

* Best Poster Award, 2021 College of Life Science Graduate Student Symposium, NTHU. (學生：碩士班 王昱婷)
* 2020 國家衛生研究院-國立清華大學聯合學術研討會 學生論文競賽 優等獎 (學生：博士班黃聖翔)
* 國立清華大學107學年度 **校級傑出教學獎 (校級)**
* 國立清華大學生命科學院107年度 院級教學優良教師 (院級).
* 國立清華大學生命科學院106年度 院級教學優良教師 (院級).
* 國立清華大學生命科學院104年度 院級教學優良教師 (院級)
* 國立清華大學104學年度 **校級傑出教學獎 (校級)**
* 2019臺灣發育生物學會與臺灣幹細胞學會聯合國際研討會**優秀論文獎** (學生：博士班梁啟榮)
* 108學年度沈巨塵先生清華獎學金 (學生：博士班梁啟榮)
* 第24屆細胞及分子生物新知研討會 (Dr. Chien-Tien Hsu’s Award in The Twenty-fourth Symposium on Recent Advances in Cellular and Molecular Biology, 2016)－**徐千田優秀論文獎** (學生：博士班張怡雯)
* Best Poster Award, 2020 College of Life Science Graduate Student Symposium, NTHU. (學生：碩士班 張庭嘉)
* Best Poster Award, 2019 College of Life Science Graduate Student Symposium, NTHU. (學生：碩士班 王馨)
* Best Poster Award, 2018 College of Life Science Graduate Student Symposium, NTHU. (學生：碩士班 謝宇鈞)
* Best Poster Award, 2017 College of Life Science Graduate Student Symposium, NTHU. (學生：碩士班 李可圈)
* Best Poster Award, 2016 College of Life Science Graduate Student Symposium, NTHU. (學生：碩士班 李可圈)

***Reviewers & Others Academic experiences***

* 研究計畫審核

竹科【109年度科學工業園區研發精進計畫】生科領域-主審委員

竹科【108年度科學工業園區研發精進計畫】書面審查委員

107-110年度教育部學海計畫書面審查委員

榮台聯大計畫審查委員

行政院科技部生命科學研究發展司計畫審查委員

財團法人工業技術研究院—工研院專利外部專家審查振興醫療財團法人振興醫院院內計畫審查委員

* 國際期刊論文審核委員

2021 Anti-Cancer Agents in Medicinal Chemistry; Combinatorial Chemistry & High Throughput Screening; Scientific Reports

2020 Oncogene; Current Pharmaceutical Biotechnology; Current Proteomics; Cell Death & Disease; Current Drug Research Reviews; BIOCELL; Life Sciences; Current Bioinformatics; Endocrine, Metabolic & Immune Disorders - Drug Target; Cancers; Anti-Cancer Agents in Medicinal Chemistry; International Journal of Molecular Medicine;

2019 Oncotarget; Chinese Journal of Physiology; Aging; Molecular Medicine Reports; Oncogene; Current Pharmaceutical Design; Oncology Reports

2018 Journal of Translational Medicine; Oncotarget; Cancer Control; Disease Markers2017 *OncoTargets and Therapy; Biochimie*