Cancer Stem Cells: Models and Concepts

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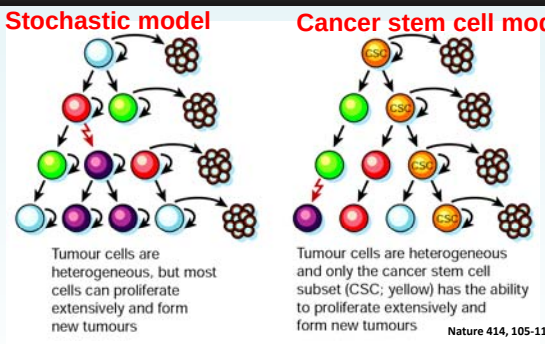
The Cancer Stem Cell (CSC) Hypothesis

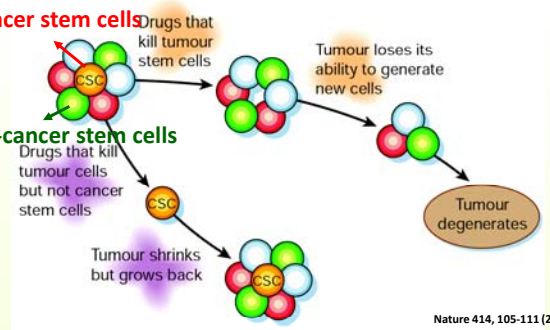
The major component of the CSC hypothesis is that tumors contain and are "driven" by cellular components that display stem cell properties. CSCs represent malignant cell subsets in hierarchically organized tumors, which are selectively capable of tumor initiation and self-renewal and give rise to bulk 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.

Two General Models of Heterogeneity in Solid Cancer Cells



Nature 414, 105-111 (2001)

The Implications of Cancer Stem Cells for Cancer Therapy



Nature 414, 105-111 (2001)

▲ **Conventional therapies may shrink tumors by killing mainly cells with limited proliferative potential. If the putative cancer stem cells are less sensitive to these therapies, then they will remain viable after therapy and re-establish the tumor. By contrast, if therapies can be targeted against cancer stem cells, then they might more effectively kill the cancer stem cells, rendering the tumors unable to maintain themselves or grow. Thus, even if cancer stem cell-directed therapies do not shrink tumors initially, they may eventually lead to cures.**

Lab Members

Diverse Targets of β-catenin during the Epithelial-Mesenchymal Transition Define Cancer Stem Cells and Predict Disease Relapse (*Cancer Research* 2015 75: 3398)

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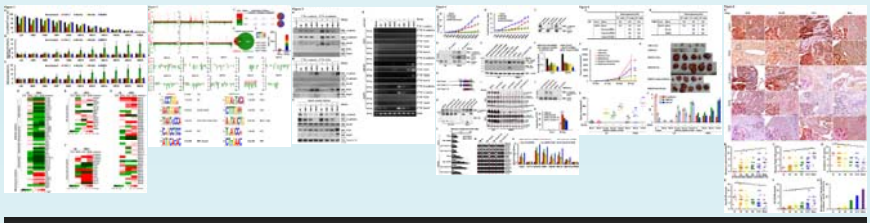

Polarized Cell Migration Induces Cancer Type-specific CD133/Integrin/Src/Akt/Gsk3β/β-catenin Signaling Required for Maintenance of Cancer Stem Cell Properties (*Oncotarget* 2015 Oct 19)

Ying-Jhen Su,[a] Wei-Hsin Lin,[a,b] Yi-Wen Chang,[a] Kuo-Chen Wei,[c] Chi-Lung Liang,[a] Shin-Cheh Chen,[d] and Jia-Lin Lee[a,e]

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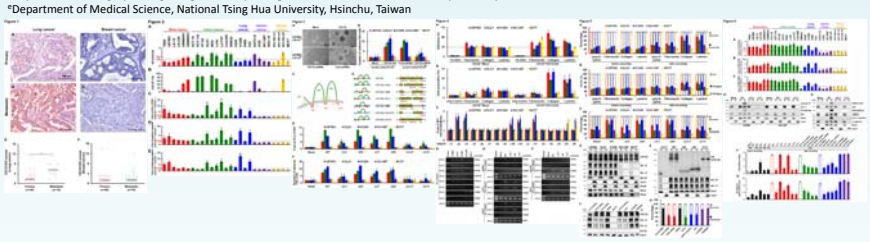

An Aberrant Nuclear Localization of E-cadherin Is A Potent Inhibitor of Wnt/β-catenin-elicited Promotion of the Cancer Stem Cell Phenotype (*Oncogenesis* 2015 4: e157)

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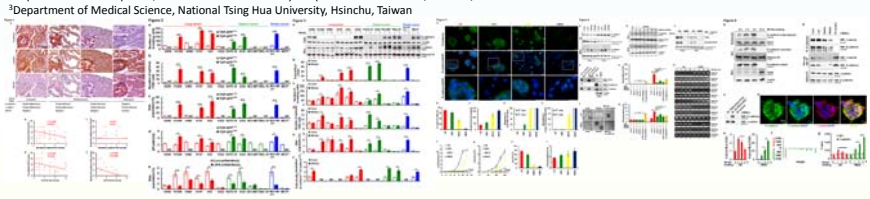
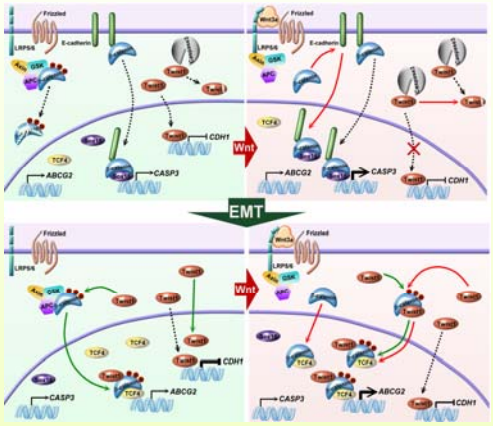
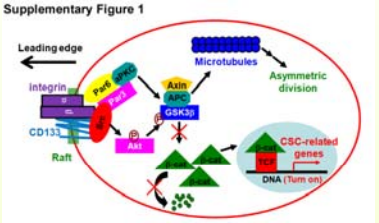


Conclusion



Wnt signaling contributes to the reprogramming and maintenance of cancer stem cell (CSC) states that is activated by the epithelial-mesenchymal transition (EMT) program. However, the mechanistic relationship between the EMT and Wnt pathway in CSCs remains unclear. Chromatin immunoprecipitation with high-throughput sequencing (ChIP-seq) indicated that the EMT induces a switch from the β-catenin/E-cadherin/Sox15 complex to the β-catenin/Twist1/TCF4 complex, which then binds to CSC-related gene promoters. In tandem co-IP and re-ChIP experiments using epithelial-type cells, Sox15 associated with the β-catenin/E-cadherin complex and then bound to the proximal promoter region of *CASP3*, consequently resulting in Twist1 cleavage and negatively regulating the β-catenin–elicited promotion of the CSC phenotype. During the EMT, Twist1 in complex with β-catenin enhanced β-catenin/TCF4 transcriptional activity, which includes binding to the proximal promoter region of *ABCG2*, a marker of CSCs. For clinical application, the five-gene signature nuclear β-catenin^{High}/nuclear Twist1^{High}/E-cadherin^{Low}/Sox15^{Low}/CD133^{High} may be a valuable prognostic marker in patients with human lung cancer.

Supplementary Figure 1



Stem cells reside in a special microenvironment called the niche. Key niche components and interactions include autocrine/paracrine growth factors, cell-cell contacts, and cell-matrix adhesions. However, the complexity and integration of these elements is far from understood. CD133 has been widely used as a surface marker to isolate cancer stem cells (CSCs), although its precise biological function remains poorly defined. By chromatin immunoprecipitation, we found that β-catenin bound to the proximal promoter regions of *ITGA2-4* and *ITGA10-11* in cell lines from brain, colon, and lung cancers, which can be triggered by CD133 expression, whereas β-catenin bound to the proximal promoter regions of *ITGB6* and *ITGB8* in cell lines from gastric and breast cancers, suggesting that CD133 induced b-catenin transcriptional activation and binding to diverse targets in cancer cells in a cancer-specific manner. To determine whether establishment of polarity and subsequent asymmetric cell division (ACD) in cancer cells is CD133/integrin dependent, we chased BrdU-labeled CD133^{+} cells cultured on ECM-coated dishes before/after wounding. In response to directional cues, integrins, Src, and the Par complex were enriched in lipid rafts, and the assembly and activation of an integrated CD133-integrin-Par signaling complex led to Src and aPKC activation. Signaling through aPKC enhanced the association of APC with microtubule plus ends followed by reorganization of the microtubule network, resulting in ACD. CD133-elicited Src activation enhanced the phosphorylation of GSK3β and its potential upstream regulator Akt. The subsequent increase and nuclear translocation of b-catenin may be a regulatory switch to increase drug resistance and stemness properties in cancer cells. Taken together, the polarized cell migration–induced CD133/integrin/Src/Akt/GSK3β/β-catenin axis is required for maintenance of CSC properties. These results establish a functional role for CD133 and support the rationale of targeting CD133 in cancer treatment.