



Biology and Drug Discovery of Cancer Stem Cells

Wen-Wei Chang

Associate Professor

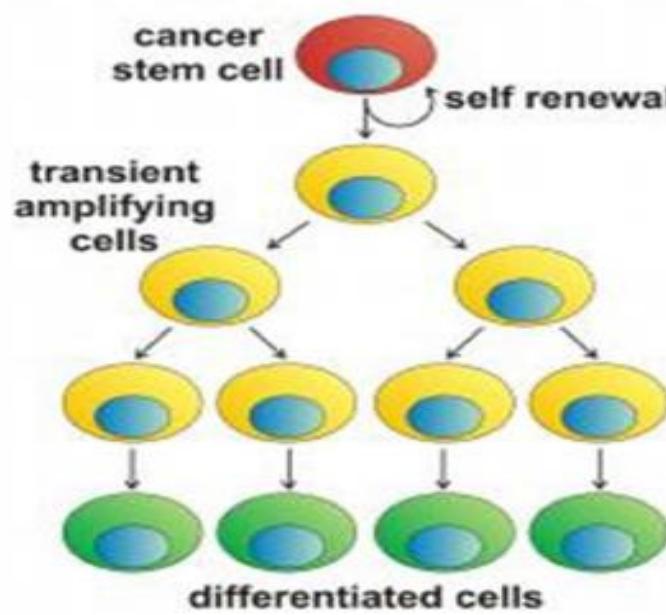
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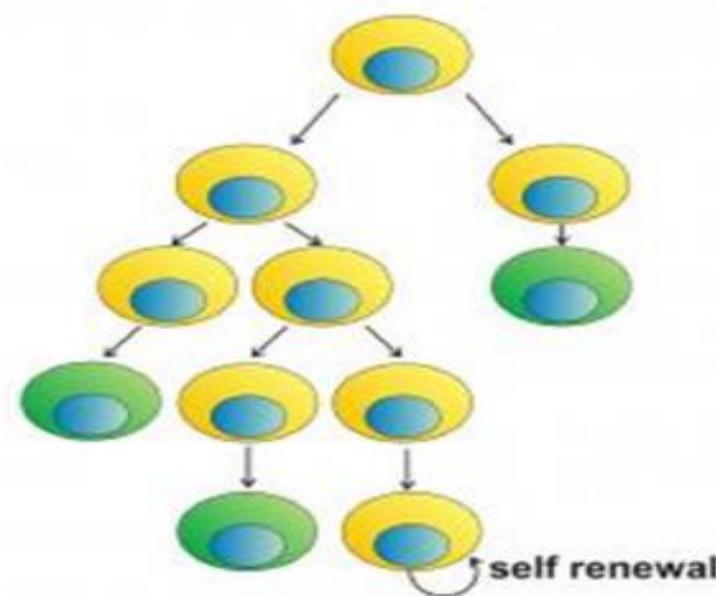


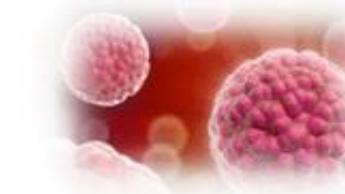
Models of heterogeneity in cancer

The cancer stem cell model



The stochastic model

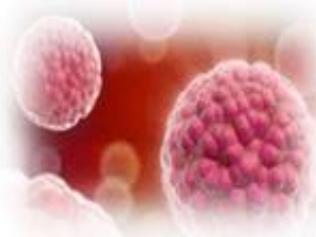




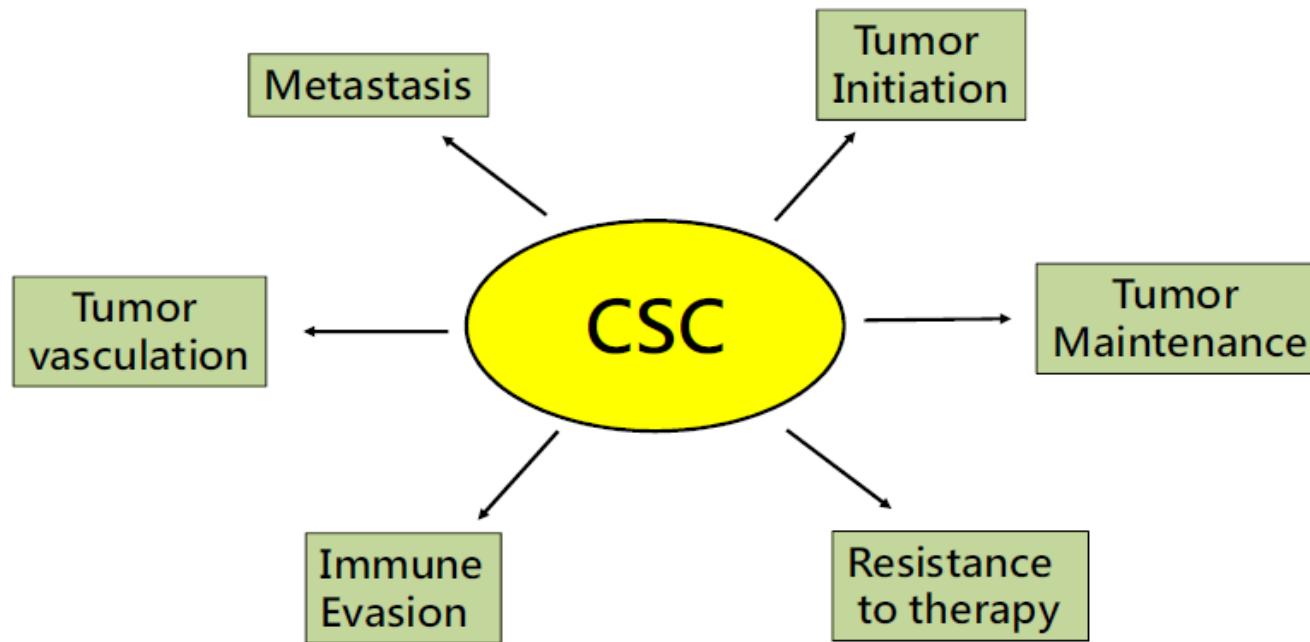
Cancer stem cells have been discovered among varieties of cancers

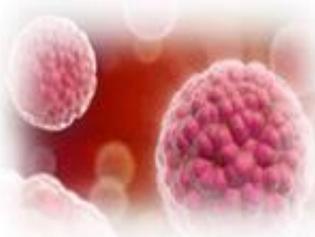
Tumour type	CSC marker	Tumour cells expressing CSC marker, %	Minimal number of cells expressing CSC markers for tumour formation	Injected in Matrigel	Transplantation site	Strain	Refs
Breast	CD44 ⁺ /CD24 ^{low}	11–35	200	+	Mammary fat pad	NOD-SCID	19
Breast	CD44 ⁺ /CD24 ⁻	ND	2×10^3	–	Mammary fat pad	NOD-SCID	77
Breast	ALDH1 ⁺	3–10	500	+ *	Mammary fat pad	NOD-SCID	33
Brain	CD133 ⁺ (GBM)	19–29	100	–	Brain	NOD-SCID	20
	CD133 ⁺ (MB)	6–21	100	–	Brain	NOD-SCID	20
Brain	CD133 ⁺	2–3	500	–	Brain	nu/nu	24
Colon	CD133 ⁺	1.8–25	200	+	Kidney capsule	NOD-SCID	26
Colon	CD133 ⁺	0.7–6	3×10^3	–	Subcutaneous	SCID	27
Colon	EpCAM ^{hi} /CD44 ⁺	0.03–38	200	+	Subcutaneous	NOD-SCID	32
Head and neck	CD44 ⁺	0.1–42	5×10^3	+	Subcutaneous	Rag2/ γ -DKO, NOD-SCID	117
Pancreas	CD44 ⁺ /CD24 ⁺ /ESA ⁺	0.2–0.8	100	+	Pancreas	NOD-SCID	65
Pancreas	CD133 ⁺	1–3	500	–	Pancreas	NMRI-nu/nu	28
Lung	CD133 ⁺	0.32–22	10^4	–	Subcutaneous	SCID	42
Liver	CD90 ⁺	0.03–6	5×10^3	–	Liver	SCID/Beige	53
Melanoma	ABCBS5 ⁺	1.6–20	10^6	–	Subcutaneous	NOD-SCID	35
Mesenchymal	Side population (Hoechst dye)	0.07–10	100	–	Subcutaneous	NOD-SCID	118

*Also injected with fibroblasts. ALDH, aldehyde dehydrogenase; CSC, cancer stem cell; EpCAM, epithelial cell adhesion molecule; ESA, epithelial specific antigen; GBM, glioblastoma multiforme; MB, medulloblastoma, ND, not determined; NOD-SCID, non-obese diabetic-severe combined immunodeficient; Rag2/ γ -DKO, Rag 2 common cytokine receptor γ -chain double knockout.



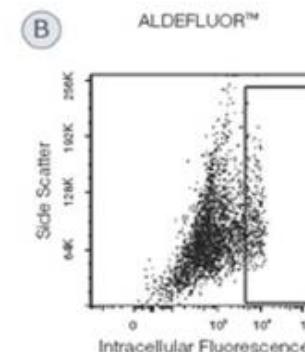
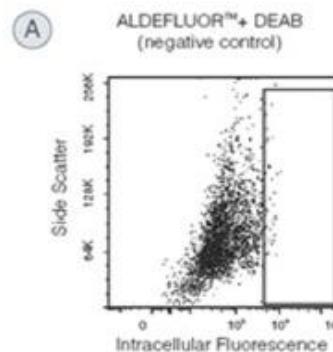
Impacts of cancer stem cells in cancer biology





How to analyze the population of cancer stem cells?

Specific markers (ALDEFLUOR assay)

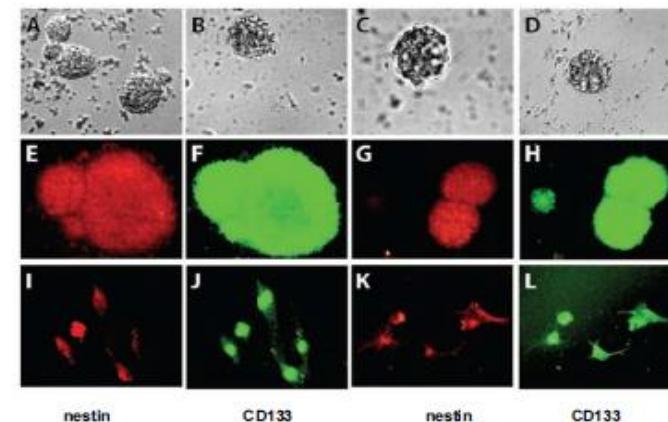


www.stemcell.com

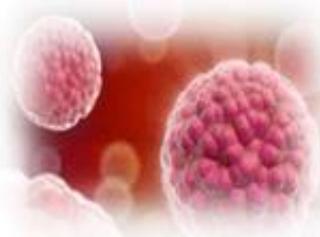
spheroid cultivation



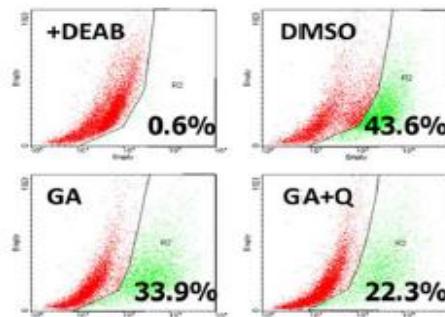
Jordan, CT. et al. NEJM. 2006. 355(12):1253-61.



CANCER RESEARCH 2003. 63:5821-5828



Drug discovery in targeting cancer stem cells

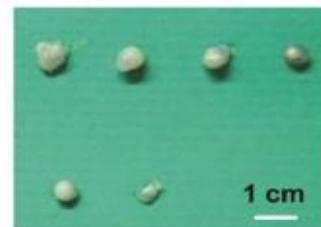


Cytotoxicity assay of candidate compounds

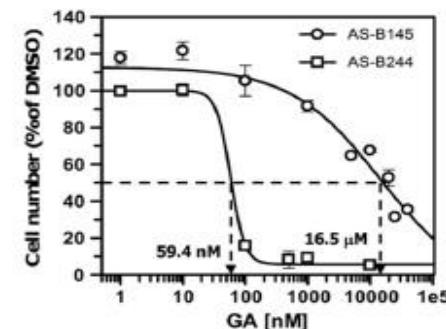
Select working concentration below IC_{50}

Marker analysis
(flow cytometry)

Spheroid cultivation
(ultralow attachment surface)



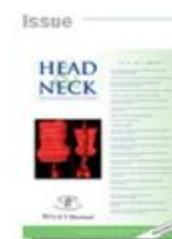
In vivo tumorigenicity assay
(Xenograftment)



Original Article

Quercetin in elimination of tumor initiating stem-like and mesenchymal transformation property in head and neck cancer

Wen-Wei Chang PhD^{1,2}, Fang-Wei Hu DDS, PhD^{3,4,†}, Cheng-Chia Yu PhD^{3,4,5,†}, Hsiu-Huan Wang BS¹, Hsiang-Pu Feng BS¹, Chih Lan BS¹, Lo-Lin Tsai DDS, PhD^{3,4} and Yu-Chao Chang DDS, PhD^{3,4,*}



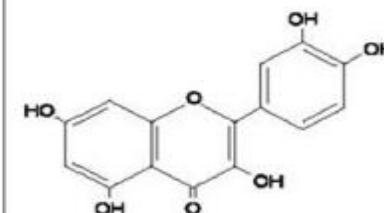
Head & Neck
Volume 35, Issue 3, pages 413–419,
March 2013

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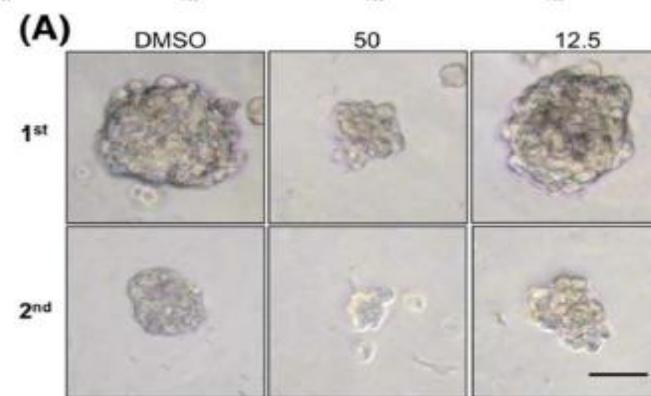
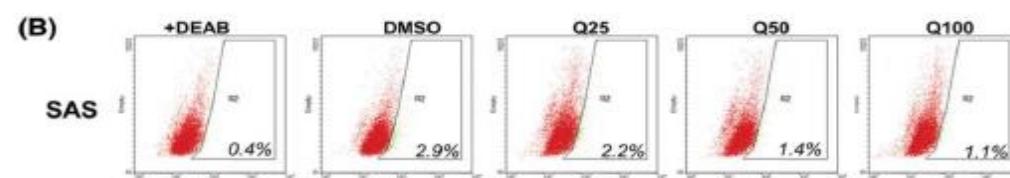
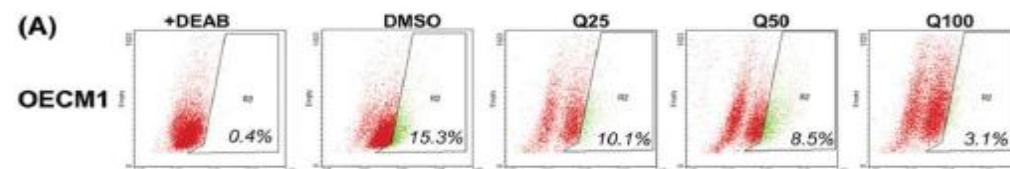
DOI: 10.1002/hed.22982

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Structure of Quercetin



<http://www.thenaturalbladder.com/>





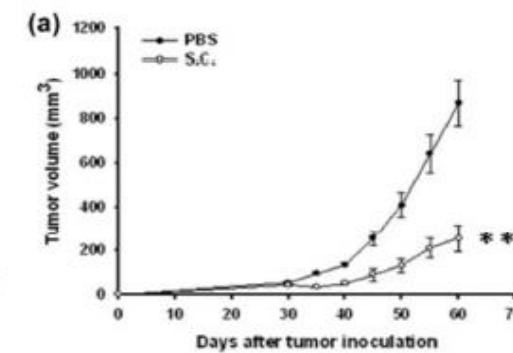
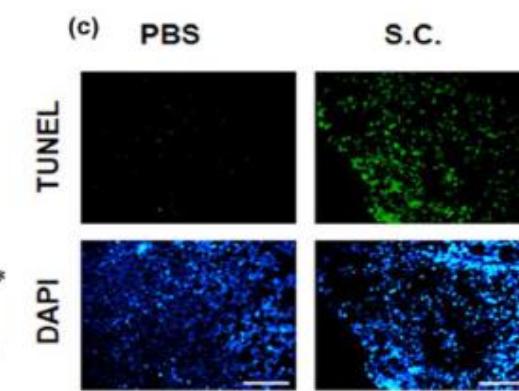
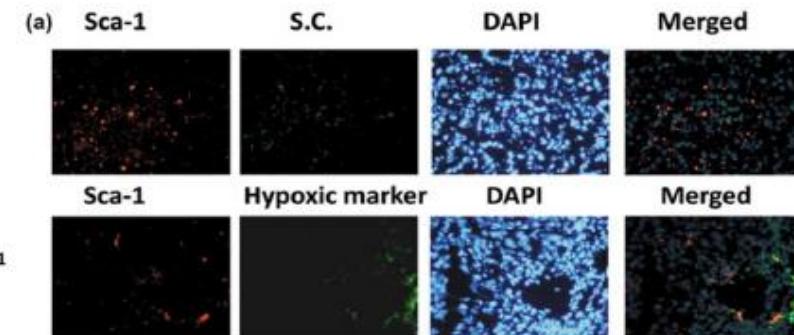
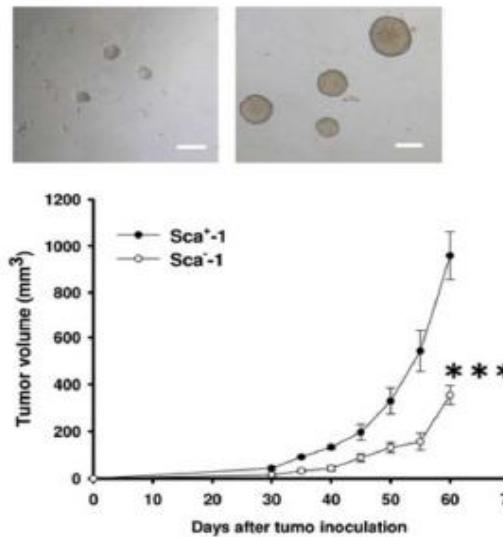
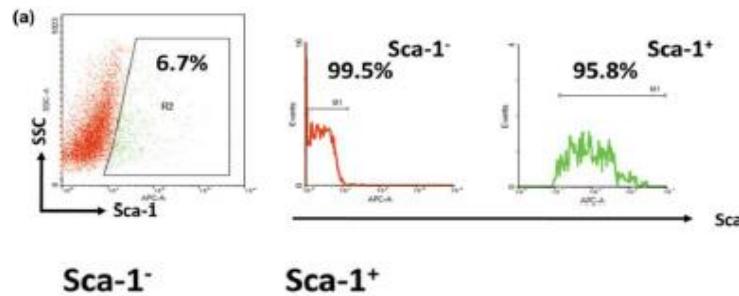
EBM

Tracking of mouse breast cancer stem-like cells with *Salmonella*

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Wei et al. *Breast Cancer Research* 2011, **13**:R101
http://breast-cancer-research.com/content/13/5/R101



RESEARCH ARTICLE

Open Access

Hsp27 participates in the maintenance of breast cancer stem cells through regulation of epithelial-mesenchymal transition and nuclear factor- κ B

Li Wei^{1,2}, Tsung-Ta Liu³, Hsiu-Huan Wang⁴, Hui-Mei Hong^{4,5}, Alice L Yu⁶, Hsiang-Pu Feng⁴ and Wen-Wei Chang^{4,5*}

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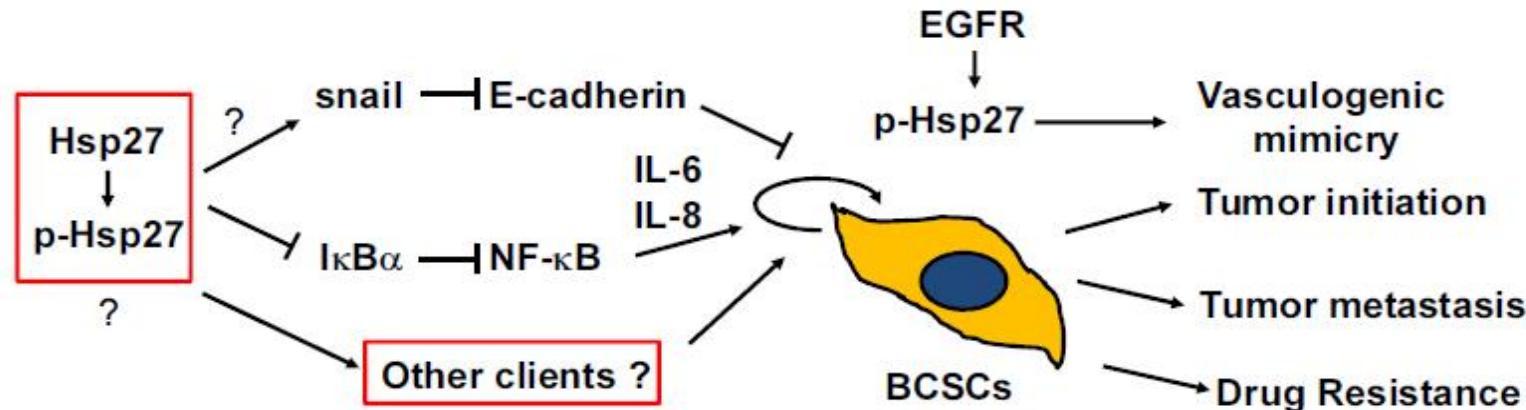
journal homepage: www.elsevier.com/locate/biochi



Research paper

Epidermal growth factor/heat shock protein 27 pathway regulates vasculogenic mimicry activity of breast cancer stem/progenitor cells

Che-Hsin Lee^{a,b}, Yu-Ting Wu^{c,f}, Hung-Chun Hsieh^{c,f}, Yun Yu^c, Alice L. Yu^{d,e},
Wen-Wei Chang^{c,f,*}



- Targeting Hsp27 may be an interesting strategy in future breast cancer therapy.