HKU Breakthrough in Identifying Cancer Stem Cells Responsible for Metastasis in Human Colorectal Cancer

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Colorectal Cancer in Hong Kong

- 2nd most common cancer in Hong Kong – over 4000 new cases per year
- Incidence rising rapidly, and expected to become the most common cancer in Hong Kong in the next few years
- 3rd and 2nd leading cause of cancer death in males and females respectively
- In 2008, 1,686 deaths were caused by colorectal cancer, accounting for 13.5% of all cancer deaths

Staging in Colorectal Cancer

- Prognosis depends on stage of cancer

Stage		5-yr survival
I	invades into muscle layer	>90%
II	invades into subserosa	55-70%
III	lymph node involvement	25-55%
IV	distant spread to other organs	8%

Metastasis in Colorectal Cancer (Stage IV)

- The process where cancer cells break off and travel through bloodstream or lymphatics and spread to a distant site
- Liver is the most common site
- Metastases may be curable with surgery
- Widely metastatic disease is treated by systemic therapies, but not usually curable

Current Treatment Regimens

- Surgery
- Adjuvant chemotherapy (for stage II and III cancers)
- Molecular targeted therapy plus chemotherapy (for unresectable metastatic disease)

Adjuvant Chemotherapy

- Even after surgery, cancer recurs and/or metastasize in > 50% of patients within 5 years
- In more advanced stage tumours, cancer cells may have spread beyond the surgical resection region, resulting in tumour recurrence
- Chemotherapy is given to patients with cancers of stage II and III after surgery to reduce the risk of recurrence / spread to distant sites

Monitoring for Cancer Recurrence

- Regular follow-up
- Colonoscopy every 2-3 years after resection
- Tumour markers- proteins produced and secreted by cancer cells into the blood may serve as an early indication of recurrent disease
  - e.g. carcinoembryonic antigen (CEA)
- Regular CT scans for patients with resection of liver metastasis

HKU Discovery

- We identified a type of cancer stem cells (CSCs) with a surface marker CD26
- These CSCs are present in all stage 4 colon cancer cells, and all liver metastatic cancer cells

HKU Discovery

- These CSCs are present in some of the stage II and stage III colon cancer cells.
- Stage II and III patients with these CSCs are more likely to have metastasis on follow up
- Stage II and III patients without these CSCs do not have metastasis on follow up

Presence of CD26+ cells in Primary Colorectal Cancer and Liver Metastasis

	CD26$^+$	CD26$^-$
Primary colorectal cancer without distant metastasis (n=27)	8	19
Stage I n=6	0	6
II n=13	1*	12
III n=8	7#	1
Colorectal cancer with synchronous liver metastasis (Dukes IV, n=5)		
Primary tumor	5	0
Liver metastasis	5	0
Metachronous liver metastasis (n=11)	11	0

* 1 patient developed metastasis after resection of primary during follow-up at 10 months

\# 4 patients developed metastasis after resection of primary during follow-up of 8-15 months.

Presence of CD26+ cells Predicts Development of Metastasis after Resection of Primary Tumours

CD26+ cells:

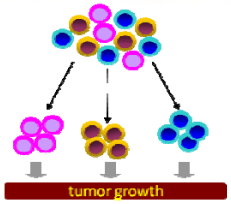
- present in all metastatic tumours
- can accurately predict development of metastasis -
  5 of 27 primary cancer patients later developed distant metastasis during follow-up, all of which have CD26+ cells present in the primary tumour

Patients without CD26+ cells:

- none of the 19 patients developed distant metastasis during follow-up

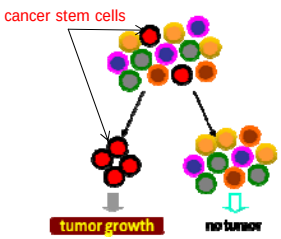
Cancer Stem Cells (CSCs)

- In the past, cancer cells were considered a homogeneous population of cells, all with the capability to proliferate and form tumour

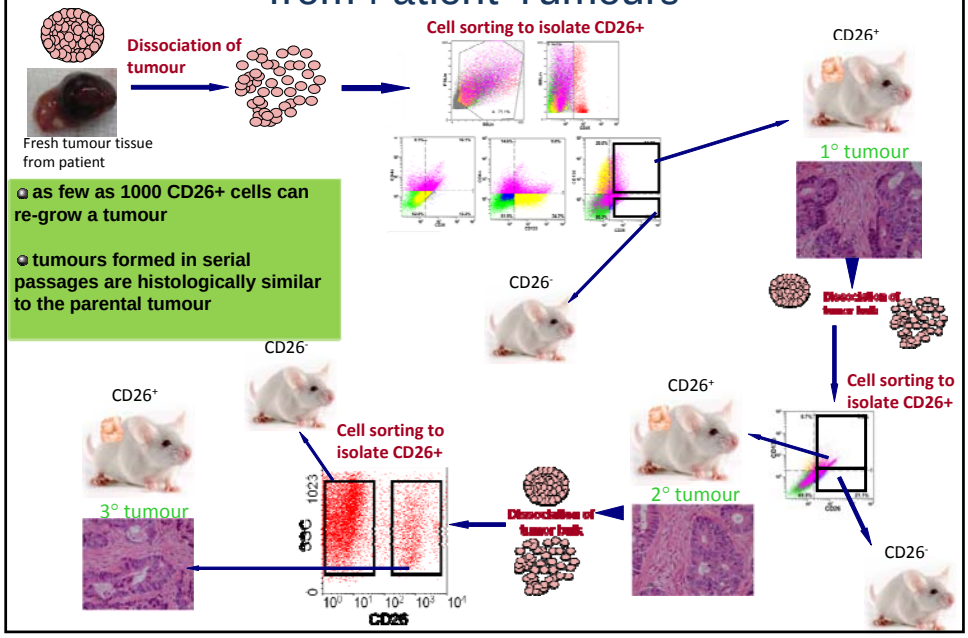


- Emerging evidence has suggested that the ability to initiate and sustain tumour growth is dependent on a small subset of cancer cells – cancer stem cells
- Similar to normal stem cells, cancer stem cells can:
  - produce further cells like themselves (self renewal)
  - differentiate to provide various different cell types (differentiation);

  leading to formation of a tumour bulk

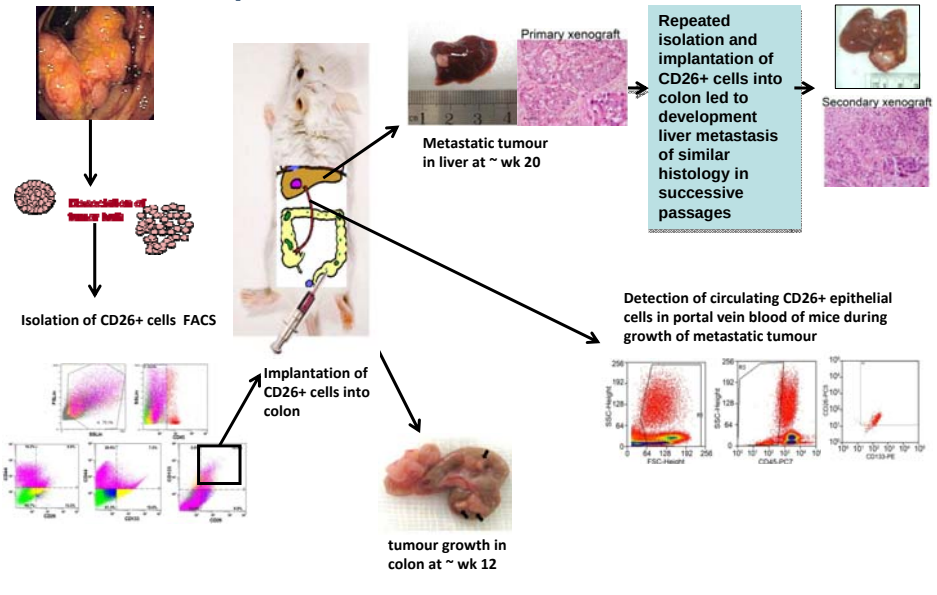


Isolation and Characterization of CD26+ Cells from Patient Tumours

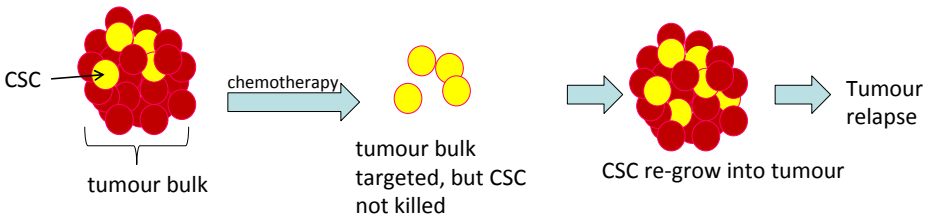


- as few as 1000 CD26+ cells can re-grow a tumour
- tumours formed in serial passages are histologically similar to the parental tumour

Development of Metastasis from Implantation of CD26+ cells



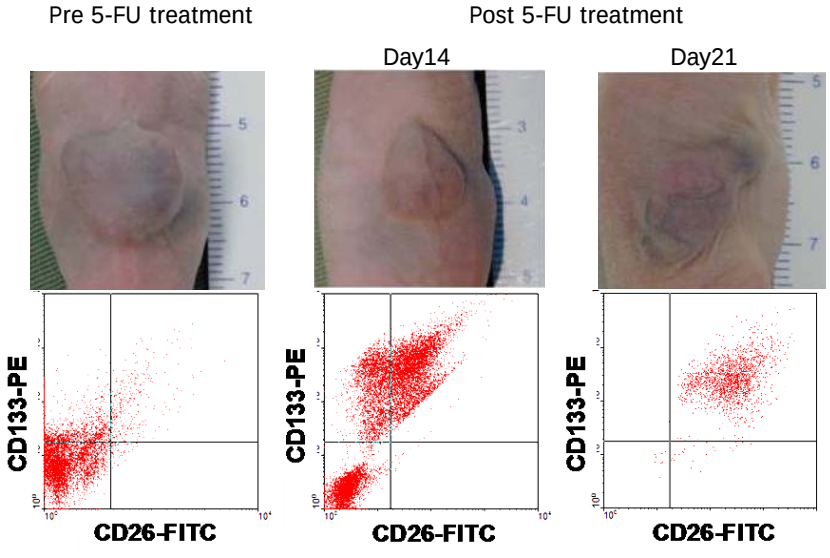
CSCs: Clue to Failure of Chemotherapy in Cancers



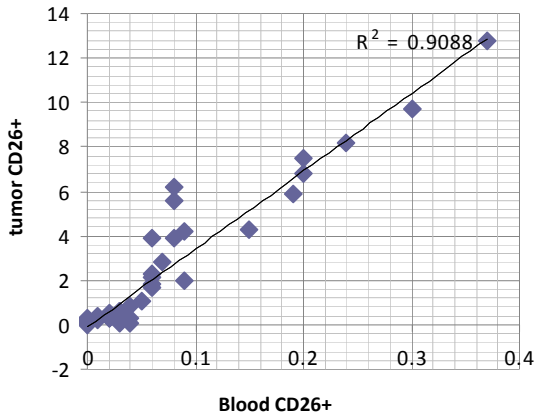
Conventional chemotherapy

- Targets all actively proliferating cells
- Non-specific
- CSCs more resistant to chemotherapy
- Tumour shrinkage ≠ all tumour cells killed

Chemotherapy leads to reduction in tumour size, but enrichment of CD26+ population



Correlation of Tumor CD26 and Blood CD26 Expression

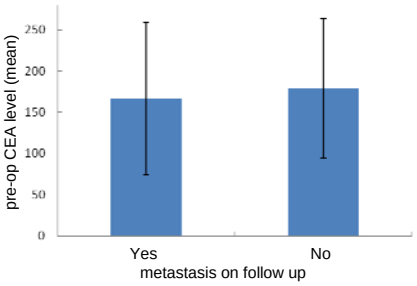


- Patients with CD26+ cells in their tumours also had CD26+ cells detected in blood

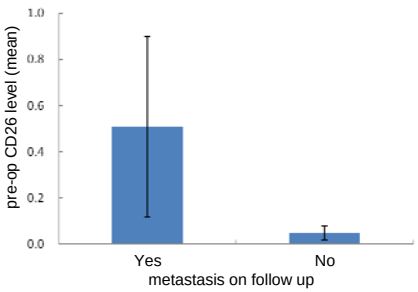
Metastasis on Follow-up (median 13.2 months)

- High preoperative CSC level, but *not* CEA level, predicts development of metastasis after resection of primary tumour

CEA Level



Circulating CD26 CSC Level



Clinical Implications

- Tumour CD26+ is a useful prognostic marker in prediction of metastasis after resection of colorectal cancer – may help to identify high risk group for adjuvant therapy
- Serial monitoring of circulating CD26 level in post-operative period may predict development of metastasis
- A potential target for development of molecular targeted therapies to more effectively eradicate all cancer cells in the tumour

Questions and Answers