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Press Release

June 4, 2010

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

The University of Hong Kong Li Ka Shing Faculty of Medicine has conducted a study on human colorectal cancer that identified for the first time a subset of cancer stem cells (CSCs) responsible for metastasis in human colorectal cancer. Metastasis is the spread of a cancer to distant organs, a stage that leads to ultimate death in most cancer patients. The novel finding of the role of a subset of CSCs in metastasis is an important breakthrough that contributes to better prognostic prediction and treatment of cancer patients in the future. The research is published in *"Cell Stem Cell"*, the top journal in stem cell research.

One of the key researchers, Dr. Roberta PANG Wen-chi, Research Assistant Professor of the Department of Medicine, HKU says, "Identification and characterization of this subpopulation of cancer stem cells will enable us to evaluate for different molecular targeting drugs that can specifically target these cells. In the long term, it should facilitate the development of more useful, safe and specific drugs that can be used in combination with chemotherapy to completely eradicate the tumour."

About colorectal cancer

Colorectal cancer is a common cancer worldwide and also one of the three most common cancers in Hong Kong, with rapidly rising incidence in recent years (over 4000 new cases per year). It is predicted that it will become the most common cancer in Hong Kong in the next few years. Surgical and chemotherapy treatments of colorectal cancer are well-established, but it remains the second most common cause of cancer-related death worldwide, suggesting that current therapies are not adequate to cure the disease.

Conventional treatment for colorectal cancer and its deficiency:

Surgical resection is the mainstay of treatment, but even with adequate surgical removal of the primary tumour, distant metastasis develop in more than 50% of patients; and despite aggressive surgical resection or chemotherapy for the metastasis, most patients eventually succumb to the metastasis. Understanding the biological mechanism of metastasis is the key to improving patient survival for this common cancer.

HKU study on cancer stem cells in colorectal cancer

Recent evidence indicates that cancers contain a small population of CSCs that are responsible for tumour initiation and maintenance; they are more resistant to conventional treatments than the more mature cancer cells within the tumour, making it difficult to completely eradicate the cancer with current therapeutic regimens.

Researchers in HKU have successfully isolated a subpopulation of cancer cells endowed with stem cell properties that are responsible for initiating metastasis. Fresh specimens of primary colorectal cancer and liver metastatic tumours resected from patients were immediately processed to isolate CSCs using a panel of surface markers. CSCs, but not mature cancer cells, are capable of regenerating tumours with similar histology to the human cancers when injected into mice. The HKU researchers identified a specific marker, CD26, which marks a subset of CSCs with metastatic capacity. CD26+ CSCs are uniformly present in both the primary and metastatic tumours in colorectal cancer patients with liver metastasis. In other patients without distant metastasis at presentation, the presence of CD26+ CSCs in their primary tumours could predict the development of distant metastasis on follow-up. Isolated CD26+ CSCs, but not CD26- CSCs, from human colorectal cancer are capable of initiating distant metastasis when implanted into the colon of the mouse model.

Treatment of mice implanted with primary colorectal cancer using chemotherapy drugs currently used for the cancer led to initial tumour shrinkage but subsequent recurrence and liver metastasis, a phenomenon frequently seen in the clinical setting. Chemotherapy treatment enriches the subpopulation of CD26+ CSCs in the tumour, which is more chemo-resistant than other cancer cells within the tumour, explaining the failure of chemotherapeutic treatment frequently observed in the clinical setting.

The ability to predict metastasis based on the CD26+ CSCs in the primary tumour as a marker of metastasis may help selection of patients for adjuvant therapy. Furthermore, the identification of this subset of CSCs provides insight into a novel strategy to target these CSCs to more effectively prevent and treat metastasis in colorectal cancer.

Further studies

The HKU research team is conducting a further study to isolate the CD26+ CSCs in the blood of colorectal cancer patients, which will facilitate a much more convenient way of using circulating CD26+ CSCs as a predictive maker of metastasis even in patients with unresectable tumours. The team is also studying the specific molecular pathways responsible for the metastatic capacity of this subset of CSCs, with the aim of developing molecular targeted drugs to effectively inhibit metastasis in colorectal cancer.

About the HKU research team:

The ground-breaking research findings of this study are the results of collaboration between the Division of Gastroenterology and Hepatology of Department of Medicine (Professor Benjamin WONG Chun-yu and Dr. Roberta PANG Wen-chi), Division of Colorectal Surgery (Professor LAW

Wai-lun) and Division of Hepatobiliary Surgery (Professor Ronnie POON Tung-ping) of Department of Surgery, Li Ka Shing Faculty of Medicine, HKU, with contribution from the Centre for Cancer Research of HKU.

About *Cell Stem Cell*:

Cell Stem Cell is a monthly journal from Cell Press launched in June 2007, which is affiliated with the International Society for Stem Cell Research (ISSCR). It publishes research articles and review materials with a focus on stem cells. The journal was named "Best New Journal" of 2007 by the Professional and Scholarly Division of the Association of American Publishers, achieving an impact factor of 16.8 in 2 years since its launch; ranking first in stem cell research and top ten in medical sciences.

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新聞稿

二零一零年六月四日

香港大學突破性發現導致大腸癌轉移的癌幹細胞

香港大學李嘉誠醫學院最近進行一項大腸癌研究，首次發現導致大腸癌轉移的癌幹細胞。癌症轉移是指腫瘤擴散至體內其他器官，是最終導致癌症病人死亡的主因。港大這項嶄新發現，有助透過預測病人完成治療後癌症轉移的機會，從而為病人提供更有效的治療方案，減低大腸癌死亡率。研究剛發表於幹細胞研究範疇最權威的學術期刊—《細胞幹細胞》*(Cell Stem Cell)*。

負責領導這項研究的香港大學李嘉誠醫學院內科學系助理教授(研究) 彭詠枝博士指：「識別這群癌幹細胞可使我們更有效地發展大腸癌的治療，研究出針對這群癌幹細胞的分子標靶療法。長遠而言，發展出更有效、安全及具針對性的殺死癌幹細胞藥物，以結合放射治療，屆時可望完全殺死腫瘤內的細胞，以降低腫瘤復發或轉移的現象。」

關於大腸癌：

大腸癌是全球最常見的癌症之一，在香港是三大常見癌症之一；近年，大腸癌發病率更有上升趨勢（每年超過四千宗新例）。根據預測，在未來數年，大腸癌將成為香港最常見的癌症。雖然大腸癌已有手術切除和化療等有效的治療方法，然而，大腸癌仍然是香港癌症的第二號殺手，意味著現有的治療未能有效地消滅癌細胞。

大腸癌傳統治療方法和缺點：

手術切除為治療大腸癌的最佳方案，但仍然會有五成以上的患者於手術後出現腸外轉移；即使對轉移腫瘤施行手術切除或化療，大多數患者最終也會死於癌症腸外轉移。因此，了解大腸癌轉移的生物學機理是提高病人生存機會的關鍵。

港大對大腸癌癌幹細胞的研究：

最近有研究顯示癌腫瘤內一小部分具有幹細胞特徵的癌細胞 — 癌幹細胞（CSCs），是誘發及維持癌腫瘤不斷生長的源頭。這些癌幹細胞比腫瘤內的其他較成熟癌細胞對傳統化療有更高抗藥性，導致目前的化療方案難以徹底治癒大腸癌。

港大研究人員成功分離出大腸癌內一群能誘發腫瘤轉移的癌幹細胞。研究人員對病人的原發性大腸癌和肝臟轉移癌手術切除的標本，利用細胞表面分子標誌物進

行癌幹細胞分離及研究。在動物實驗中，這群癌幹細胞擁有「自我更生」的能力，可以再生出與原病人相同的腫瘤，而腫瘤內其他癌細胞則沒有此能力。此研究更發現大腸癌內一群表達 CD26+標誌的癌幹細胞具有轉移的能力。於所有肝臟轉移的大腸癌病人，包括其原發性腫瘤的標本以及肝臟轉移腫瘤的標本內，均具有 CD26+癌幹細胞。至於尚未出現腸外轉移的大腸癌患者，其原發性腫瘤若有 CD26+癌幹細胞，也可預測到患者日後會發展腸外轉移。當 CD26+癌幹細胞植入缺乏免疫力鼠的大腸後，不但可再生成跟原始腫瘤特性相同的腫瘤，而且更會誘發肝臟轉移。

使用化療藥物治療植入大腸癌的小鼠起初可令腫瘤縮小，但之後會出現腫瘤復發和肝臟轉移，與臨床現象相同。研究顯示化療藥令腫瘤內的 CD26 +癌幹細胞群增多，而 CD26+癌幹細胞比腫瘤內的其他癌細胞抗藥性更高，導致在臨床上化療藥難以徹底消滅大腸癌腫瘤。

這個研究首次證明在大腸癌中有一群癌幹細胞會引致癌症轉移。CD26+癌幹細胞預測轉移的能力，臨牀上可應用於選擇病人術後接受輔助治療。此外，通過研究這群癌幹細胞的分子特性，可望發展出能夠更有效地抑制大腸癌轉移的標靶藥物。

進一步研究：

研究小組正進一步在大腸癌患者血液中分離 CD26+癌幹細胞，以期可以令一些未能透過做手術切除的大腸癌病人，更方便地使用血液中 CD26+幹細胞作為預測轉移的標誌物。研究小組亦正在研究 CD26+癌幹細胞導致大腸癌轉移的分子途徑，最終希望能夠研發出有效抑制大腸癌轉移的標靶藥。

香港大學研究小組：

這項突破性的研究，是香港大學李嘉誠醫學院內科學系腸胃肝臟內科（王振宇教授及彭詠枝博士），聯同外科學系結直腸外科（羅偉倫教授）和肝膽胰外科（潘冬平教授）共同合作的成果，並得到香港大學癌症研究中心的支持。

有關《細胞幹細胞》期刊：

《細胞幹細胞》*（Cell Stem Cell）*是細胞出版社（Cell Press）旗下的國際學術月刊及國際幹細胞研究學會（ISSCR）所屬期刊，於 2007 年 6 月開始出版，刊登有關幹細胞研究的文章。《細胞幹細胞》獲美國出版商協會的專業及學術分支選為 2007 年度「最佳新學術刊物」。於發行後的短短兩年間，《細胞幹細胞》的影響系數已達 16.8，在幹細胞研究期刊排名榜中高居首位，而在醫學期刊中亦位列十大。

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