c-Met in pancreatic cancer stem cells: Therapeutic implications

Marta Herreros-Villanueva, Aizpea Zubia-Olascoaga, Luis Bujanda

Abstract
Pancreatic cancer is the deadliest solid cancer and currently the fourth most frequent cause of cancer-related deaths. Emerging evidence suggests that cancer stem cells (CSCs) play a crucial role in the development and progression of this disease. The identification of CSC markers could lead to the development of new therapeutic targets. In this study, the authors explore the functional role of c-Met in pancreatic CSCs, by analyzing self-renewal with sphere assays and tumorigenicity capacity in NOD SCID mice. They concluded that c-Met is a novel marker for identifying pancreatic CSCs and c-Met can be a higher tumorigenic cancer cell population. Inhibition of c-Met with XL184 blocks self-renewal capacity in pancreatic CSCs. In pancreatic tumors established in NOD SCID mice, c-Met inhibition slowed tumor growth and reduced the population of CSCs, along with preventing the development of metastases.

Key words: Cancer stem cells; c-Met; Gemcitabine; Self-renewal; Tumorigenicy

Peer reviewers: Ferruccio Bonino, MD, PhD, Professor of Gastroenterology, Director of General Medicine 2nd Unit, Director of Liver and Digestive Disease Division, Department of Internal Medicine, University Hospital of Pisa, University of Pisa, via Roma 67, 56124 Pisa, Italy; Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief of Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, 5901 E. Seventh Str., Long Beach, CA 90822, United States

Herreros-Villanueva M, Zubia-Olascoaga A, Bujanda L. c-Met in pancreatic cancer stem cells: Therapeutic implications. World J Gastroenterol 2012; 18(38): 5321-5323 Available from: URL: http://www.wjgnet.com/1007-9327/full/v18/i38/5321.htm DOI: http://dx.doi.org/10.3748/wjg.v18.i38.5321

INVITED COMMENTARY ON HOT ARTICLES
Pancreatic adenocarcinoma is one of the most aggressive neoplasias and the fourth leading cause of cancer death in the United States, with 5 year survival being less than 5%[1]. Part of the reason for the fatal prognoses of patients with pancreatic adenocarcinoma is the lack of response to the available therapies. In addition to achieving early diagnosis, the identification of markers for prognosis and response to therapy is necessary for the development of specific targeting agents for the management of patients with pancreatic cancer[2].

Conventional chemotherapy is directed at tumor cells that have limited tumorigenic potential, instead of targeting the cancer stem cell population.

Cancer stem cells (CSCs) conform to a subpopulation of tumoral cells that contribute mainly to drug resistance; since they can self-renew indefinitely and are charac-
terized by their relative quiescence. These properties, together with the contribution of the epithelial to mesenchymal transition, allow them to avoid conventional chemotherapy induced-cell death, and thus patients often suffer from tumor relapse.\(^3,4\)

A better understanding and characterization of these cells will be a helpful tool in the future for designing new therapies, since the CSC hypothesis predicts that only therapies that efficiently eliminate the CSC fraction of a tumor are able to induce long-term response and halt tumor progression. Novel therapeutic strategies that could target pancreatic CSCs will allow us to induce drug sensitivity, the inhibition of invasion, and the metastasis of pancreatic cancer, which will ultimately yield better treatment outcomes.\(^5\)

Although there have many studies attempting to establish markers for these CSCs, there is no complete or defined panel for the identification of these cells. Isolated CSCs have been reported to show increased tumorigenicity, chemoresistance, stationary phase, and asymmetric division to differentiate into non-stem progeny.\(^6,7\) Based on these characteristics, pancreatic CSCs are identified by flow cytometry using cell surface markers such as CD44, CD24, ESA, CD133, ALDH1 and low proteosome activity.\(^8-13\)

In this study, new data is presented about CSC characterization and possible related therapies that should be considered for pancreatic cancer clinical trials.

c-Met is a receptor of the tyrosine kinase family that acts as a proto-oncogene and is stimulated by hepatocyte growth factor to mediate motility, invasion, and metastasis.\(^14\) The levels of c-Met are increased in pancreatic carcinoma where c-Met signaling induces growth and invasion. Some authors have reported c-Met as a stem cell marker in pancreatic tissue,\(^15\) as well as in other tissues and organs such as the brain and gastrointestinal tract where the molecule regulates stem cell proliferation and cell renewal.\(^16,17\)

In this study, the authors conclude that c-Met is a novel marker for pancreatic CSCs and they show the functional role of this molecule in pancreatic tumors.

Using xenografts (immunodeficient mice NOD-SCID) and injecting pancreatic cancer cells from patients, they show that there is a subpopulation of cells that express high levels of c-Met (c-Met\(^{\text{high}}\)) while another subpopulation expresses low levels or does not express this marker at all (c-Met\(^{\text{low}}\)). Part of the c-Met\(^{\text{high}}\) population also expresses other previously described CSCs markers such as CD44, CD24, CD133, and ALDH1, but compared with these other markers, c-Met\(^{\text{high}}\) is better at identifying higher tumorigenic cancer cell populations.\(^5\) When injecting the same number of cells, c-Met\(^{\text{high}}\) cells produce tumors in 35% of the mice, while CD133\(^{\text{+}}\) produces tumors in 16% and CD44\(^{\text{+}}\) in 25%.

The population of positive cells for both the markers c-Met and CD44 (c-Met\(^{\text{high}}\)/CD44\(^{\text{+}}\)) enhances the in vivo tumorigenicity compared with the population with CD44\(^{\text{+}}\) alone. These data together show that c-Met is an important and novel marker of pancreatic CSCs.

Using sphere formation assay, it can be shown that c-Met\(^{\text{high}}\) cells have a self-renewal capacity, as they can form tumorspheres while c-Met\(^{\text{low}}\) are unable to do so.

On the other hand, treatment with the chemical inhibitor XL184 (a small molecule kinase inhibitor for c-Met) or the inhibition of c-Met with a specific shRNA impairs sphere formation, leading to apoptosis and cell cycle arrest; showing that c-Met activity is required to maintain a CSC population. XL184 inhibits tumor growth and reduces the number of CSCs in xenograft mice with subcutaneous tumors and in orthotopic models.

When compared with Gemcitabine, the effect produced by XL184 is different. Although both XL184 alone and Gemcitabine alone treatments can inhibit tumor growth during the period that the animal is receiving treatment, some days after the end of treatment, the tumor growth continues at the same rate as the control tumors. By contrast, when the treatments are combined (XL184 in combination with Gemcitabine), tumor growth is prevented for up 32 d following cessation of treatment. This effect is due to the cells that each treatment targets. While Gemcitabine treatment results in an increase of the c-Met\(^{\text{high}}\)/CD44\(^{\text{+}}\) population (likely because these cells are resistant to cell death with this chemotherapy) c-Met inhibition with XL184 leads to a decrease in c-Met\(^{\text{high}}\)/CD44\(^{\text{+}}\) cells. Combination treatment prevents the increase in the CSC population observed with Gemcitabine alone and also contributes to a decrease in c-Met\(^{\text{high}}\)/CD44\(^{\text{+}}\) population, suggesting that XL184 targets the CSC population specifically. Additionally, using an intracardiac injection model with pancreatic cancer cells, the authors demonstrated that XL184 treatment prevents metastasis development.

A study by Li et al\(^8\) contributes significantly to the investigation into the stemness of pancreatic cancer cells. The study in question shows that c-Met is a new human pancreatic CSC marker. The results demonstrate that, in addition to identifying the population of cells with a self-renewal capacity in a pancreatic tumor, c-Met is a molecule necessary for maintaining tumoral cell growth and has capacity for metastasize.

Previous experiments had characterized CSCs as EpCAM\(^{\text{+}}\), CD44\(^{\text{+}}\), CD24\(^{\text{+}}\), CD133\(^{\text{+}}\), low proteosome activity, ALDH1\(^{\text{+}}\) for pancreatic CSCs, and CD133\(^{\text{+}}\)/CXCR4\(^{\text{+}}\) for CSCs with higher metastatic potential. The addition of the new marker c-Met, already identified in other types of tumor, directs research towards the development of therapies targeting this tyrosine kinase receptor. In addition to its role as a biomarker of pancreatic CSCs, the authors propose a potential therapy, showing reduced tumor growth in xenograft mice. They also demonstrated that c-Met has an important role in metastasis development, and that this process could be blocked by targeting c-Met specifically with XL184 treatment. XL184 (Cabozantinib) is a small-molecule kinase inhibitor with potent activity toward c-Met and vascular endothelial growth factor (VEGF).
factor receptor 2, as well as a number of other receptor tyrosine kinases including rearranged during transfection, kinase receptor, axl receptor tyrosine kinase, and fms like tyrosine kinase 3[8].

The authors demonstrated that XL184 targeting c-Met could be a promising therapy in combination with Gemcitabine treatment for pancreatic cancer. This is a very important achievement, since pancreatic cancer has a fatal prognosis due to its resistance to the currently available chemotherapy and radiotherapy. Although Gemcitabine is the most common chemotherapy used in pancreatic cancer patients, it has been demonstrated that it may not be particularly useful due to the properties that CSCs confer to the tumor. Some studies have demonstrated that, after Gemcitabine treatment, the subpopulation of CSC CD133+ is enriched[9] and that pancreatic cancer cell lines can undergo epithelial to mesenchymal transition after this treatment, resulting in an increased population of CD44+CD24+ESA+ cells[9].

Li et al[10] showed that the combination treatment of XL184 and Gemcitabine is an effective therapy for pancreatic cancer treatment. As different studies have shown, using a combination of therapies that target CSCs and the non-tumorigenic population of pancreatic cancer cells, this neoplasia can be effectively treated.

Collectively, these data and other recently published studies concerning different tumors, suggest that c-Met is a promising CSC marker for pancreatic cancer and XL184 is effective at inhibiting tumor growth, angiogenesis, and metastasis, and both should be seriously considered for clinical trials in combination with other available chemotherapy.

REFERENCES

1 Jemal A, Siegel R, Xu J, Ward E. Cancer statistics, 2010. CA Cancer J Clin 2010; 60: 277-300
2 Ansari D, Chen BC, Dong L, Zhou MT, Andersson R. Pancreatic cancer: translational research aspects and clinical implications. World J Gastroenterol 2012; 18: 1417-1424
3 Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 2003; 100: 3983-3988
4 Krantz SB, Shields MA, Dangi-Garimella S, Munshi HG, Bentrem DJ. Contribution of epithelial-to-mesenchymal transition and cancer stem cells to pancreatic cancer progression. J Surg Res 2012; 173: 105-112
5 Li Y, Kong D, Ahmad A, Bao B, Sarkar FH. Pancreatic cancer stem cells. Emerging target for designing novel therapy.

Cancer Lett 2012; Epub ahead of print
6 Haraguchi N, Iishi H, Mimori K, Tanaka F, Ohkuma M, Kim HM, Akita H, Takiuchi D, Hatano H, Nagano H, Barnard GF, Doki Y, Mori M. CD13 is a therapeutic target in human liver cancer stem cells. J Clin Invest 2010; 120: 3326-3339
7 Neumüller RA, Knoblich JA. Dividing cellular asymmetry: asymmetric cell division and its implications for stem cells and cancer. Genes Dev 2009; 23: 2675-2699
8 Li C, Lee CJ, Simeone DM. Identification of human pancreatic cancer stem cells. Methods Mol Biol 2009; 568: 161-173
9 Adikrisna R, Tanaka S, Muramatsu S, Aihara A, Ban D, Ochiai T, Irie T, Kudo A, Nakamura N, Yamaoka S, Airi S. Identification of pancreatic cancer stem cells and selective toxicity of chemotherapeutic agents. Gastroenterology 2012; 143: 234-45.e7
10 Li C, Heidt DG, Dalerba P, Burant CF, Zhang L, Adsay V, Wicha M, Clarke MF, Simeone DM. Identification of pancreatic cancer stem cells. Cancer Res 2007; 67: 1030-1037
11 Herrmann PC, Huber SL, Herrler T, Aicher A, Ellwart JW, Guba M, Bruns CJ, Heeschen C. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. Cell Stem Cell 2007; 1: 313-322
12 Lonardo E, Herrmann PC, Heeschen C. Pancreatic cancer stem cells - update and future perspectives. Mol Oncol 2010; 4: 431-442
13 Kim MP, Fleming JB, Wang H, Abbruzzese JL, Choi W, Kopetz S, McConkey DJ, Evans DB, Gallick GE. ALDH activity selectively defines an enhanced tumor-initiating cell population relative to CD133 expression in human pancreatic adenocarcinoma. PLoS One 2011; 6: e20636
14 Michieli P, Mazzone M, Basilico C, Cavassa S, Sottile A, Naldini L, Comoglio PM. Targeting the tumor and its microenvironment by a dual-function decoy Met receptor. Cancer Cell 2004; 6: 61-73
15 Suzuki A, Nakauchi H, Taniguchi H. Prospective isolation of multipotent pancreatic progenitors using flow-cytometric cell sorting. Diabetes 2004; 53: 2143-2152
16 Di Renzo MF, Narsimhan RP, Olivero M, Brett S, Giordano S, Medico E, Gaglia P, Zara P, Comoglio PM. Expression of the Met/HGF receptor in normal and neoplastic human tissues. Oncogene 1991; 6: 1997-2003
17 Nicoleau C, Benzekour O, Agasse F, Thiriet N, Petit J, Prestoz L, Roger M, Jaber M, Coronas V. Endogenous hepatocyte growth factor is a niche signal for subventricular zone neural stem cell amplification and self-renewal. Stem Cells 2009; 27: 408-419
18 Yakes FM, Chen J, Tan J, Yamaguchi K, Shi Y, Yu P, Qian F, Chu F, Bentzien F, Cancilla B, Orf J, You A, Laird AD, Engst S, Lee L, Lesch J, Chou YC, Joly AH. Cabozantinib (XL184), a novel MET and VEGFR2 inhibitor, simultaneously suppresses metastasis, angiogenesis, and tumor growth. Mol Cancer Ther 2011; 10: 2298-2308
19 Shah AN, Summy JM, Zhang J, Park SI, Parikh NU, Gallick GE. Development and characterization of gemcitabine-resistant pancreatic tumor cells. Ann Surg Oncol 2007; 14: 3629-3637

S-Editor Gou SX  L-Editor Rutherford A  E-Editor Zhang DN