EBioMedicine 39 (2019) 29–30

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

EBioMedicine
Published by THE LANCET

Commentary

High Endothelial Venules and Pancreatic Ductal Adenocarcinoma: A potential game changer

Shu Ming Chai [a,b], Ser Yee Lee [b,c,*]

[a] Singapore Eye Research Institute, Singapore National Eye Centre, Singapore
[b] Duke - National University of Singapore (NUS) Medical School, Singapore
[c] Department of Hepatopancreatobiliary and Transplant Surgery, Singapore General Hospital, Singapore

Pancreatic Ductal Adenocarcinoma (PDAC) is a highly lethal disease with its annual incidence rate almost mirroring its mortality rate [1]. There were 55,440 new cases of PDAC and 44,330 deaths in the United States last year alone and it continues to be a growing problem worldwide [1]. Majority (>80%) of patients will present with unresectable disease and for those with metastases on diagnosis, the 5-year survival is a dismal 5% or less [2,3]. Even in patients with early or resectable disease, the surgery is plagued by complexity, complications and significant recurrence rate, even in high-volume expert centers [3,4]. Despite some advances in the understanding of the molecular and genetic basis of pancreatic cancer, the results and prognosis remains much to be desired.

Nonetheless, exciting new therapeutics are in development and there is light for better outcomes in the future [2]. Our understanding of PDAC's biology has evolved, notably in various fields such as tumor microenvironment (TME), cancer immunology and genetics. One of the hurdles and central to the failures of cytotoxic-based regimens such as gemcitabine and FOLFIRINOX (folinic acid, 5-FU, irinotecan and oxaliplatin) is the notorious dense stroma composing a significant portion of the tumor and an intense desmoplastic reaction, serving as a barrier impairing drug delivery and supporting an immunosuppressive TME. [2]. It is clear that new strategies are necessary and some strides have been made in different aspects. Stromal modifying therapy using enzymes such as recombinant pegylated hyaluronidase enzyme to target tumor stromal hyaluronan have shown early promise in Phase I and II studies [2]. Another emerging method to tackle the immmuosuppressive TME is by targeting and/or inhibiting various chemokines. Targeted therapy has shown little efficacy in PDAC beyond erlotinib and gemcitabine. Most targeted therapy has been directed at the RAS pathway and/or platelet/epidermal-derived growth factor receptors (PDGFR/EGFR). Other downstream effectors such as MEK, ERK and ERK, various cell-cycle checkpoint inhibitors and novel kinase receptors are currently being studied as targets for inhibition as well. Other pronged approaches includes immunotherapy strategies such as anti-CTLA-4, anti-PD-1, Chimeric antigen receptor T cells (CAR-T) and monoclonal antibodies [2]. Another approach worth mentioning are those targeting anti-metabolism and DNA repair processes [2].

As a pancreatic surgical oncologist and a cancer researcher, I read with great interest the study by Bahmani et al. titled: Ectopic High Endothelial Venules in Pancreatic Ductal Adenocarcinoma: A Unique Site for Targeted Delivery, and congratulate them on conducting an elegant study and sharing their promising findings [5]. High Endothelial Venules (HEVs) are specialized post-capillary venules found in the paracortical areas of lymph nodes (LNs) and they are distinct functionally and morphologically from ordinary venules; they are first characterized in the field of immunology [6]. These studies suggest that HEV pay a central role in lymphocyte trafficking to LNs. More recently, interest in HEVs been centered around cancer research as it has been shown that in the presence of a cancer and before the arrival of metastasis in the sentinel LNs (SLN), there were reorganizations of vasculature and lymphatic vessels in the primary tumor and SLN; these remodeled and prominent blood vessels were identified as modified HEV [6–9]. Bahmani and colleagues demonstrated that HEVs form de novo in PDAC and engineered MECA79-coated nanoparticles (MECA79-NPs) that recognize these ectopic HEVs in PDAC. Utilizing a tumor implantation mouse model and nano-techniques, they demonstrated that treatment with MECA79-Taxol-NPs improved the efficacy of Paclitaxel (Taxol) significantly in suppressing the growth of PDAC [5]. Though a small and early study, it provided an important proof of concept and an innovative strategy. We have previously reported and demonstrated the metamorphosis of HEV in a TME and described that the HEV transformation starts from a normal immunological mediator to a tumor/tumor metastasis mediator. This was reflected by morphological changes in a spectrum from a normal appearing HEV, to a dilated HEV, and then to one containing red blood cells. We and others have further correlated the HEV changes and its vessel density with the clinical outcomes [6–9]. In fact, it was shown that in the presence of cancer, in the microenvironment, the HEV becomes the predominant blood vessels in the primary tumor as well as the LNs [7–9]. Others studies' findings have also supported the hypothesis that HEV transforms and presumably functions like a blood vessel in anticipation to supply the needs for an accelerating growth of a tumor or a soon-to-arrive tumor deposit in the draining LNs and thus opens up a potential novel therapeutic approach [6–9].

DOI of original article: https://doi.org/10.1016/j.ebiom.2018.11.030.
* Corresponding author at: Department of Hepatopancreatobiliary and Transplant Surgery, Singapore General Hospital, The Academia, 20 College Road, 169856, Singapore.
E-mail address: lee.ser.yee@singhealth.com.sg (S.Y. Lee).

https://doi.org/10.1016/j.ebiom.2018.11.061

Occasionally when two emerging technologies or fields serendipitously engages and combines their knowledge, leaps in innovation can be achieved. Although, it may not be obvious to most at that point of time, just as only few had heard of the “Angler” phone which was launched in 1992 by IBM and Bellsound/AT&T, now in retrospect, it was the birth of the ubiquitous smartphone we can't live without today. This study which utilized HEV-MECA79 as a targeted way of getting the chemotherapeutic agents as nanoparticles through a previously almost- impenetrable barrier, in our opinion, feels like the “Angler phone” moment – a small but significant leap in anti-PDAC treatment and a potential game- changer. Bahmani and colleagues have utilized and combined the knowledge learned from two promising and emerging fields to deliver drugs that may work on a formidable and almost-incurable disease [5,10].

These findings will need further studies to validate and progress our benchside understanding to real-world bedside treatment for our patients. This heralds exciting times ahead and encourages all physicians who treat the incurable.

Disclosure

The authors declare that they have no conflict of interest and there was no financial support.

References

[1] American Cancer Society. Cancer facts & figures 2018. Atlanta: American Cancer Society. Retrieved from https://www.cancer.org/research/cancer-facts-statistics/all-cancer-facts-figures/cancer-facts-figures-2018; 2018, Accessed date: 23 November 2018.
[2] Krantz BA, Yu KH, O'Reilly EM. Pancreas adenocarcinoma: Novel therapeutics. Chin Clin Oncol 2017;6(3):30.
[3] Yeo CJ, Cameron JL, Lillemoe KD, et al. Pancreaticoduodenectomy for cancer of the head of the pancreas: 201 patients. Ann Surg 1995;221:721–3.
[4] Sadot E, Brennan M, Lee SY, et al. Readmission after pancreatic resection: Causes and causality pattern. Ann Surg Oncol Dec, 2014;21(13):4342–50.
[5] Bahmani B, Uehara M, Ordikhani F, et al. Ectopic high endothelial venules in pancreatic ductal adenocarcinoma: A unique site for targeted delivery. EBioMedicine 2018. https://doi.org/10.1016/j.ebiom.2018.11.030.
[6] Jones E, Gallimore A, Ager A. Defining high endothelial venules and tertiary lymphoid structures in cancer. Methods Mol Biol 1845;2018:99–118.
[7] Lee SY, Chao-Nan Q, Seng OA, et al. Changes in specialized blood vessels in lymph nodes and their role in cancer metastasis. J Transl Med 2012;10:206.
[8] Qian C, Berghuis B, Tsarfaty G, et al. Preparing the "soil": The primary tumor induces vasculature reorganization in the sentinel lymph node before the arrival of metastatic cancer cells. Cancer Res Nov, 2006;66(21):10365–76.
[9] Lee SY. Alterations of high endothelial venules in primary and metastatic tumors are correlated with lymph node metastasis of oral and pharyngeal carcinoma. Cancer Biol Ther Apr 22, 2014;15(7).
[10] Giordano G, Pancione M, Olivieri N, et al. Nano albumin bound-paclitaxel in pancreatic cancer: Current evidences and future directions. World J Gastroenterol August 28, 2017;23(32):5875–86.