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Gut Microbiome and Antitumor Immunity: A Cross Talking in Pancreatic Cancer

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Gut microbiome is a group of microbe population inhabiting in gastrointestinal tract; with majority of the population being bacteria, and small proportion of virus and fungi [1]. Recent advance research focused on understanding the role of gut microbiome in human health and disease, these research finding described the correlation of role of gut microbiome in onset and progression of clinical conditions. Microbiome has been extensively studied for its role in digestion of food, metabolism and assimilation of food-derived nutrients. However, imbalance in microbiome composition disturbs normal physiological state, resulting in many clinical conditions, particularly in cancer [2-4]. To elucidate the role of gut microbiome in tumor progression, recent studies and publications suggest gut microbiome plays important roles in tumor associated immune response. Dysbiosis of gut microbes may also increase risk of tumor generation in various types of cancer. However, alteration of gut microbiome composition regulates the efficacy of anti-cancer therapy through modulation of anti-tumor immune responses. Gut microbiome mediated modulation of tumor microenvironment is implicated with immune check point receptors and ligands blockade-based immunotherapy efficacy. Commensal bacteria *Bifidobacterium* could promote antitumor immune responses, therefore increase anti-PD-L1 immunotherapy efficacy in the murine model of melanoma [5]. In melanoma patients gut microbiota modulated the therapeutic responses to anti-PD-1 immunotherapy [6]. In a recent study demonstrated that PD-1-based immunotherapy relies on intact gut microbiome, increased abundance of *Akkermansia muciniphila* impaired the efficacy of anti-PD-1 immunotherapy against epithelial tumors [7]. Another report suggested that the efficacy of anti-CTLA4 against melanoma was enhanced with higher concentrations of *Bacteroides fragilis* in guts in both melanoma mouse models and patients [8].

Pancreatic ductal adenocarcinoma (PDA) is the 3rd most lethal malignancy in US, representing a significant therapeutic challenge [9]. The association between gut microbiota and the onset of pancreatic cancer has been established for emerging therapeutic interventions to control PDA cancer progression. In 2015, a clinical investigation reported that *Fusobacterium* species in gut microbiota are involved in the higher mortality in patients with PDA [10]. Recently, there are two independent studies describing that gut microbiota play a role in promoting PDA progression; more mechanisms to underlying cross-talking between microbiota and PDA were uncovered by utilizing mice model [11,12].

George Miller's research group [11] found that gut microbiota could migrate into pancreatic tissue, and higher abundance of bacteria was found in fully grown pancreatic tumor tissue, compared to healthy pancreas. Fluorescence labeled bacteria was orally administered into mice by gavage, and migration of bacteria was monitored by detecting fluorescence signal in pancreatic tissue. This data showed direct evidence for gut microbiota accessing to pancreases was shown in the study. Comparison of pancreatic microbiome between healthy samples and PDA samples indicated more abundant bacteria in pancreatic tumor tissue. Further, repopulation experiments show that gut microbiome from PDA-bearing mice more easily translocate to pancreases compared to gut microbiota from normal mice. Using different PDA mice models, microbiota ablation has been consistently shown to suppress tumor growth. As a logical extension, clear differences were observed in composition of both gut microbiota and pancreatic microbiota between PDA and healthy human subjects. Furthermore, selected bacterial species were found to be differentially increased in PDA tumor tissue in comparison with the gut. Altogether, these findings strongly suggested specific bacterial species in microbiota play an important role in onset and progression of PDA. This study suggested that anti-tumor immunity was associated with gut

microbiota. Further, when microbiota was ablated by antibiotics in PDA mice model, tumor infiltrating T cells were increased, and suppressed myeloid-derived suppressor cell (MDSC) cells population. More essentially, phenotype of tumor associated macrophage was modulated to drive the shift from immune suppressive M2 to anti-tumor M1, which may dictate effector CD8 T cell activation in tumor microenvironment.

Independently, Vikas Dudeja group has been reported similar findings that gut microbiota depletion suppresses tumor progression in mouse model of pancreatic cancer [12]. In this study, the gut microbiome was depleted by using cocktail of oral antibiotics. After depletion of gut microbiota the fecal analysis showed that 2 phyla majorly found in mouse and human gut: the microbial species *Bacteroidetes* and *Firmicutes* were significantly decreased, reversely *Proteobacteria* and *Tenericutes* were found to be more abundant. Further, a clear decrease in pancreatic tumor burden was observed in gut bacteria depletion group compared to that in control group. Mechanistically, the T cells and B cells may be required for tumor-suppressing effect, evidenced by that *Rag1* knockout mice lacking mature T and B lymphocytes abolished this effect in same experiment. These data also suggest IL-17a plays a critical role in microbiota depletion mediated tumor growth inhibition. The mechanism still unknown how gut microbiota depletion enhance anti-tumor immune responses in tumor microenvironment.

Curative therapy for cancer has been being a challenge for almost one century, even with countless studies [13-17]. Several interesting studies focused on cross-talk between gut microbiome and anti-tumor immunity, relationship between gut microbiome and pancreatic cancer has been uncovered gradually. Manipulation-of-gut-microbiome-based therapeutic strategy against pancreatic cancer is promising and precise identification of microbiome species which impact pancreatic cancer progression will be an important target to invest on.

References

1. Ley RE, Peterson DA, Gordon JI (2006) Ecological and evolutionary forces shaping microbial diversity in the human intestine. Cell 124: 837-848.
2. Wang Z, Klipfell E, Bennett BJ, Koeth R, Levison BS, et al. (2011) Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 472: 57.
3. Kosiewicz MM, Dryden GW, Chhabra A, Alard P (2014) Relationship between gut microbiota and development of T cell associated disease. FEBS lett 588: 4195-4206.
4. Liu R, Hong J, Xu X, Feng Q, Zhang D, et al. (2017) Gut microbiome and serum metabolome alterations in obesity and after weight-loss intervention. Nat Med 23: 859.
5. Sivan A, Corrales L, Hubert N, Williams JB, Aquino-Michaels K, et al. (2015) Commensal Bifidobacterium promotes antitumor immunity and facilitates anti-PD-L1 efficacy. Sci 350: 1084-1089.
6. Gopalakrishnan V, Spencer CN, Nezi L, Reuben A, Andrews MC, et al. (2018) Gut microbiome modulates response to anti–PD-1 immunotherapy in melanoma patients. Sci 359: 97-103.
7. Routy B, Le Chatelier E, Derosa L, Duong CP, Alou MT, et al. (2018) Gut microbiome influences efficacy of PD-1–based immunotherapy against epithelial tumors. Sci 359: 91-97.
8. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, et al. (2015) Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Sci 350: 1079-1084.
9. Steele CW, Karim SA, Leach JD, Bailey P, Upstill-Goddard R, et al. (2016) CXCR2 inhibition profoundly suppresses metastases and augments immunotherapy in pancreatic ductal adenocarcinoma. Cancer Cell 29: 832-845.
10. Mitsuhashi K, Nosho K, Sukawa Y, Matsunaga Y, Ito M, et al. (2015) Association of Fusobacterium species in pancreatic cancer tissues with molecular features and prognosis. Oncotarget 6: 7209-7220.
11. Pushalkar S, Hundeyin M, Daley D, Zambirinis CP, Kurz E, et al. (2018) The pancreatic cancer microbiome promotes oncogenesis by induction of innate and adaptive immune suppression. Cancer Disc 8: 403-416.
12. Sethi V, Kurtom S, Tarique M, Lavania S, Malchiodi Z, et al. (2018) Gut microbiota promotes tumor growth in mice by modulating immune response. Gastroenterol 155: 33-37.
13. Liu D, Qi X, Manjunath Y, Kimchi ET, Ma L, et al. (2018) Sunitinib and Sorafenib modulating antitumor immunity in hepatocellular cancer. J Immunol Res Ther 3: 115-123.
14. Li G, Liu D, Kimchi ET, Kaifi JT, Qi X, et al. (2018) Nanoliposome C6-ceramide increases the anti-tumor immune response and slows growth of liver tumors in mice. Gastroenterol 154: 1024-1036.
15. Li G, Liu D, Cooper TK, Kimchi ET, Qi X, et al. (2017) Successful chemoimmunotherapy against hepatocellular cancer in a novel murine model. J Hepatol 66: 75-85.
16. Qi X, Lam SS, Liu D, Kim DY, Ma L, et al. (2016) Development of InCVAX, in situ cancer vaccine, and its immune response in mice with hepatocellular cancer. J Clin Cell Immunol 7.
17. Qi X, Li G, Liu D, Motamarry A, Huang X, et al. (2015) Development of a radiofrequency ablation platform in a clinically relevant murine model of hepatocellular cancer. Cancer Biol Ther 16: 1812-1819.