Tumor Microenvironment

In the relatively short history of anti-tumor treatment, numerous medications have been developed against a variety of targets. Intriguingly, although many anti-tumor strategies have failed in their clinical trials, metformin, an anti-diabetic medication, demonstrated anti-tumor effects in observational studies and even showed its synergistic potential with immune checkpoint inhibitors (ICIs) in subsequent clinical studies. Looking back from bedside-to-bench, it may not be surprising that the anti-tumor effect of metformin derives largely from its ability to rewire aberrant metabolic pathways within the tumor microenvironment. As one of the most promising breakthroughs in oncology, ICIs were also found to exert their immune-stimulatory effects at least partly via rewiring metabolic pathways. These findings underscore the importance of correcting metabolic pathways to achieve sufficient anti-tumor immunity. Herein, we start by introducing the tumor microenvironment, and then we review the implications of metabolic syndrome and treatments for targeting metabolic pathways in anti-tumor therapies. We further summarize the close associations of certain aberrant metabolic pathways with impaired anti-tumor immunity and introduce the therapeutic effects of targeting these routes. Lastly, we go through the metabolic effects of ICIs and conclude an overall direction to manipulate metabolic pathways in favor of anti-tumor responses.

1. The Tumor Microenvironment and Immune Checkpoint Inhibitors

Of all diseases, cancer has long been one of the major health concerns in spite of extensive research exploring ways to tackle it. Due to its abnormal growth and deadly metastasis irrespective of limited oxygen and nutrients, the deregulating cellular energetics and the immunoevasion nature of cancer have been identified, which are largely derived from its ability to recruit normal cells that constitutively create the "tumor microenvironment" (TME) [1]. The TME is characterized by a complex interplay between tumor cells and their surrounding neighbors, including stromal cells, extracellular matrix, adipocytes, mesenchymal stem cells, blood vessels, macrophages, T cells, B cells, cytokines, exosomes and metabolites. All the components within the TME contribute to building a 3-dimensional structure with gradients of oxygen tension and availability to nutrients (as shown in Figure 1) [2][3], which favors the development of tumors in multiple aspects such as local progression and distal metastasis [4][5][6][7][8][9]. Importantly, although immune cells are known to protect us from tumors through their immunosurveillance and tumoricidal nature [10][11], multiple factors within the TME may not only hinder their antitumor function but also skew them to construct an immunosuppressive environment in favor of tumor growth.
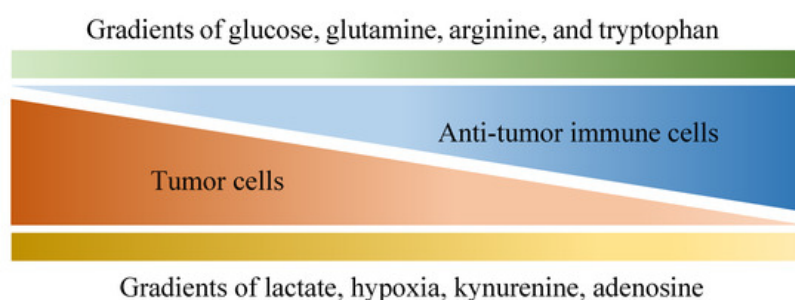
Figure 1. Various gradients within the tumor microenvironment that are differentially associated with anti-tumor activity and tumor growth. Tumor cells are known for their aberrant metabolic activity that leads to local depletion of a variety of nutrients, including glucose, glutamine, arginine and tryptophan, which effectively hinder anti-tumor activities provided by immune cells that also depend on these nutrients. In addition, metabolites such as lactate, kynurenine and adenosine are released by tumor cells, dampening anti-tumor immunity along with hypoxia.

In the devastating battlefield against tumors, a variety of protumoral factors and immunosuppressive mechanisms have been identified, of which the immunosuppressive cells, exosomes and the co-inhibitory signals play central roles to allow tumor progression. To begin with, the immunomodulatory cells, including but not limited to regulatory T (Treg) cells and M2 macrophages, accumulate in the TME and diminish T cell anti-tumor immune responses [12][13]. Treg cells are famous for their immunosuppressive effects on not only aberrant immune responses against self-antigens but also anti-tumor immune responses, in both laboratory and clinical studies [14][15][16]. Treg cells are believed to modulate immune responses through expressing immunosuppressive cytokines (including transforming growth factor (TGF)-β, interleukin (IL)-10, IL-35), immune checkpoints (such as cytotoxic T-lymphocyte-associated antigen (CTLA)-4; programmed death (PD)-1) and other co-inhibitory receptors, as extensively reviewed by previous studies [17][18]. Furthermore, Treg cells are also capable of inducing tolerogenic dendritic cells (DCs) that are linked to T cell exhaustion, and can release cytotoxic agents such as perforin and granzyme [19][20][21][22][23]. Therefore, the aberrant accumulation of Treg cells in TME impairs anti-tumor immunity through various mechanisms [24][25], facilitating tumor growth and progression. Besides Treg cells, the unwanted immunosuppression within the TME can also be affected by tumor-associated macrophages (TAMs) that are majorly driven by cytokines such as IL-4 or IL-13, which have also earned their "M2-like" naming [26][27][28]. Orchestrated by signals from tumor cells, T cells as well as stroma [29][30], TAMs play a protumoral role in the TME by promoting tumor metastasis through promoting angiogenesis as well as extracellular matrix remodeling [31][32]. Moreover, TAMs also exert their profound immunosuppressive effects through expressing a variety of inhibitory ligands and cytokines, including PD-L1, PD-L2, B7-1, B7-2, HLA-G, HLA-E, IL-10 as well as TGF-β, as clearly reviewed by previous studies [33][34]. Besides immunosuppressive cells, previous studies further reveal the vital roles of exosomes and co-inhibitory molecules to promote tumor growth and metastasis in many different ways.

The aberrant accumulation of immunosuppressive cells within the TME is thought to be affected by both exosomes and co-inhibitory signals derived from the tumor cells. Exosomes are extracellular vesicles with bi-layered membrane that range between 30-100 nm in diameter [35], while patients with cancer, especially of the ones with poor prognosis, are often found with higher numbers of them [36]. Tumor-derived exosomes have been detected in many different types of cancers, and they can not only impair anti-tumor immunity within the TME but also educate bone marrow-derived progenitor cells to facilitate distant metastasis [37][38][39][40]. On the other hand, the expression of co-inhibitory molecules such as PD-L1 have been observed on various kinds of cancer cells [41], which correlates with poor clinical outcomes of many patients with cancer [42][43]. Importantly, since the co-inhibitory checkpoint molecules expressed by both tumors and immunosuppressive cells within the TME dampens anti-tumor immunity of T cells [44][45][46][47], immune checkpoint inhibitors (ICIs) such as the antibodies directed against CTLA-4, PD-1 and PD-L1, are developed into encouraging treatments against various tumors, most notably melanoma and non-small cell lung cancer [48][49][50][51]. For instance, a pooled meta-analysis assessing long-term survival of 1861 advanced melanoma patients estimated a 3-year survival rate of 22% for patients receiving anti-CTLA4 ipilimumab [52], which evidently outperformed other chemotherapy such as dacarbazine, where the 3-year survival rates were only around 12% [53]. However, despite the game-changing efficacies of ICIs against tumors in clinical scenarios, they still face improvable downsides, including the suboptimal long-term response rates due to both innate and acquired resistance [54], as well as the lack of a reliable predictive biomarker [55]. Therefore, a variety of combinatory therapeutic strategies, along with the discovery of potential biomarkers, have been tested out to overcome the limitations, and targeting the metabolic pathways within the TME has appeared as one of the emerging candidates that have synergistic potential.

References

1. Hanahan, D.; Weinberg, R.A. Hallmarks of cancer: the next generation. cell 2011, 144, 646–674.

2. Zhang, Y.; Ertl, H.C. Starved and asphyxiated: how can CD8+ T cells within a tumor microenvironment prevent tumor progression. Front. Immunol. 2016, 7, 32.

3. Gilkes, D.M.; Semenza, G.L.; Wirtz, D. Hypoxia and the extracellular matrix: drivers of tumour metastasis. Nat. Rev. Cancer 2014, 14, 430–439.

4. Meseure, D.; Alsibai, K.D.; Nicolas, A. Pivotal role of pervasive neoplastic and stromal cells reprogramming in circulating tumor cells dissemination and metastatic colonization. Cancer Microenviron. 2014, 7, 95–115.

5. Alkasalias, T.; Moyano-Galceran, L.; Arsenian-Henriksson, M.; Lehti, K. Fibroblasts in the tumor microenvironment: shield or spear? Int. J. Mol. Sci. 2018, 19, 1532.

6. Poltavets, V.; Kochetkova, M.; Pitson, S.M.; Samuel, M.S. The role of the extracellular matrix and its molecular and cellular regulators in cancer cell plasticity. Front. Oncol. 2018, 8, 431.

7. Almendros, I.; Gileles-Hillel, A.; Khalyfa, A.; Wang, Y.; Zhang, S.X.; Carreras, A.; Farré, R.; Gozal, D. Adipose tissue macrophage polarization by intermittent hypoxia in a mouse model of OSA: effect of tumor microenvironment. Cancer Lett. 2015, 361, 233–239.

8. Wang, M.; Zhao, J.; Zhang, L.; Wei, F.; Lian, Y.; Wu, Y.; Gong, Z.; Zhang, S.; Zhou, J.; Cao, K. Role of tumor microenvironment in tumorigenesis. J. Cancer 2017, 8, 761.

9. Ghajar, C.M.; Peinado, H.; Mori, H.; Matei, I.R.; Evason, K.J.; Brazier, H.; Almeida, D.; Koller, A.; Hajjar, K.A.; Stainier, D.Y. The perivascular niche regulates breast tumour dormancy. Nat. Cell Biol. 2013, 15, 807–817.

10. Dunn, G.P.; Bruce, A.T.; Ikeda, H.; Old, L.J.; Schreiber, R.D. Cancer immunoediting: from immunosurveillance to tumor escape. Nat. Immunol. 2002, 3, 991–998.

11. Fridman, W.H.; Pagès, F.; Sautes-Fridman, C.; Galon, J. The immune contexture in human tumours: impact on clinical outcome. Nat. Rev. Cancer 2012, 12, 298–306.

12. Mellman, I.; Coukos, G.; Dranoff, G. Cancer immunotherapy comes of age. Nature 2011, 480, 480–489.

13. Balkwill, F.; Mantovani, A. Inflammation and cancer: back to Virchow? Lancet 2001, 357, 539–545.

14. Nishikawa, H.; Sakaguchi, S. Regulatory T cells in cancer immunotherapy. Curr. Opin. Immunol. 2014, 27, 1–7.

15. Sakaguchi, S.; Yamaguchi, T.; Nomura, T.; Ono, M. Regulatory T cells and immune tolerance. Cell 2008, 133, 775–787.

16. deLeeuw, R.J.; Kost, S.E.; Kakal, J.A.; Nelson, B.H. The prognostic value of FoxP3+ tumor-infiltrating lymphocytes in cancer: a critical review of the literature. Clin. Cancer Res. 2012, 18, 3022–3029.

17. Shevach, E.M. Mechanisms of foxp3+ T regulatory cell-mediated suppression. Immunity 2009, 30, 636–645.

18. Schmidt, A.; Oberle, N.; Krammer, P.H. Molecular mechanisms of treg-mediated T cell suppression. Front. Immunol. 2012, 3, 51.

19. Engelhardt, J.J.; Boldajipour, B.; Beemiller, P.; Pandurangi, P.; Sorensen, C.; Werb, Z.; Egeblad, M.; Krummel, M.F. Marginating dendritic cells of the tumor microenvironment cross-present tumor antigens and stably engage tumor-specific T cells. Cancer Cell 2012, 21, 402–417.

20. Cao, X.; Cai, S.F.; Fehniger, T.A.; Song, J.; Collins, L.I.; Piwnica-Worms, D.R.; Ley, T.J. Granzyme B and perforin are important for regulatory T cell-mediated suppression of tumor clearance. Immunity 2007, 27, 635–646.

21. Veldhoen, M.; Moncrieffe, H.; Hocking, R.J.; Atkins, C.J.; Stockinger, B. Modulation of dendritic cell function by naive and regulatory CD4+ T cells. J. Immunol. 2006, 176, 6202–6210.

22. Grossman, W.J.; Verbsky, J.W.; Barchet, W.; Colonna, M.; Atkinson, J.P.; Ley, T.J. Human T regulatory cells can use the perforin pathway to cause autologous target cell death. Immunity 2004, 21, 589–601.

23. Yan, Z.; Garg, S.K.; Banerjee, R. Regulatory T cells interfere with glutathione metabolism in dendritic cells and T cells. J. Biol. Chem. 2010, 285, 41525–41532.

24. Vignali, D.A.; Collison, L.W.; Workman, C.J. How regulatory T cells work. Nat. Rev. Immunol. 2008, 8, 523–532.

25. Wang, H.; Franco, F.; Ho, P.-C. Metabolic regulation of Tregs in cancer: opportunities for immunotherapy. Trends Cancer 2017, 3, 583–592.

26. DeNardo, D.G.; Barreto, J.B.; Andreu, P.; Vasquez, L.; Tawfik, D.; Kolhatkar, N.; Coussens, L.M. CD4+ T cells regulate pulmonary metastasis of mammary carcinomas by enhancing protumor properties of macrophages. Cancer Cell 2009, 16, 91–102.

27. Shiao, S.L.; Ruffell, B.; DeNardo, D.G.; Faddegon, B.A.; Park, C.C.; Coussens, L.M. TH2-polarized CD4+ T cells and macrophages limit efficacy of radiotherapy. Cancer Immunol. Res. 2015, 3, 518–525.

28. De Monte, L.; Wörmann, S.; Brunetto, E.; Heltai, S.; Magliacane, G.; Reni, M.; Paganoni, A.M.; Recalde, H.; Mondino, A.; Falconi, M. Basophil recruitment into tumor-draining lymph nodes correlates with Th2 inflammation and reduced survival in pancreatic cancer patients. Cancer Res. 2016, 76, 1792–1803.

29. Kumar, V.; Cheng, P.; Condamine, T.; Mony, S.; Languino, L.R.; McCaffrey, J.C.; Hockstein, N.; Guarino, M.; Masters, G.; Penman, E. CD45 phosphatase inhibits STAT3 transcription factor activity in myeloid cells and promotes tumor-associated macrophage differentiation. Immunity 2016, 44, 303–315.

30. Franklin, R.A.; Liao, W.; Sarkar, A.; Kim, M.V.; Bivona, M.R.; Liu, K.; Pamer, E.G.; Li, M.O. The cellular and molecular origin of tumor-associated macrophages. Science 2014, 344, 921–925.

31. Sangaletti, S.; Di Carlo, E.; Gariboldi, S.; Miotti, S.; Cappetti, B.; Parenza, M.; Rumio, C.; Brekken, R.A.; Chiodoni, C.; Colombo, M.P. Macrophage-derived SPARC bridges tumor cell-extracellular matrix interactions toward metastasis. Cancer Res. 2008, 68, 9050–9059.

32. Nucera, S.; Biziato, D.; De Palma, M. The interplay between macrophages and angiogenesis in development, tissue injury and regeneration. Int. J. Dev. Biol. 2011, 55, 495–503.

33. Noy, R.; Pollard, J.W. Tumor-associated macrophages: from mechanisms to therapy. Immunity 2014, 41, 49–61.

34. Mantovani, A.; Marchesi, F.; Malesci, A.; Laghi, L.; Allavena, P. Tumour-associated macrophages as treatment targets in oncology. Nat. Rev. Clin. Oncol. 2017, 14, 399.

35. Johnstone, R.M.; Adam, M.; Hammond, J.; Orr, L.; Turbide, C. Vesicle formation during reticulocyte maturation. Association of plasma membrane activities with released vesicles (exosomes). J. Biol. Chem. 1987, 262, 9412–9420.

36. Kim, H.K.; Song, K.; Park, Y.; Kang, Y.; Lee, Y.; Lee, K.; Ryu, K.; Bae, J.; Kim, S. Elevated levels of circulating platelet microparticles, VEGF, IL-6 and RANTES in patients with gastric cancer: possible role of a metastasis predictor. Eur. J. Cancer 2003, 39, 184–191.

37. Kharaziha, P.; Ceder, S.; Li, Q.; Panaretakis, T. Tumor cell-derived exosomes: a message in a bottle. Biochim. Et Biophys. Acta (Bba)-Rev. Cancer 2012, 1826, 103–111.

38. Peinado, H.; Alečković, M.; Lavotshkin, S.; Matei, I.; Costa-Silva, B.; Moreno-Bueno, G.; Hergueta-Redondo, M.; Williams, C.; García-Santos, G.; Ghajar, C.M. Melanoma exosomes educate bone marrow progenitor cells toward a pro-metastatic phenotype through MET. Nat. Med. 2012, 18, 883.

39. Quail, D.F.; Joyce, J.A. Microenvironmental regulation of tumor progression and metastasis. Nat. Med. 2013, 19, 1423.

40. Zhang, H.-G.; Grizzle, W.E. Exosomes: a novel pathway of local and distant intercellular communication that facilitates the growth and metastasis of neoplastic lesions. Am. J. Pathol. 2014, 184, 28–41.

41. Gatalica, Z.; Snyder, C.; Maney, T.; Ghazalpour, A.; Holterman, D.A.; Xiao, N.; Overberg, P.; Rose, I.; Basu, G.D.; Vranic, S. Programmed cell death 1 (PD-1) and its ligand (PD-L1) in common cancers and their correlation with molecular cancer type. Cancer Epidemiol. Prev. Biomark. 2014, 23, 2965–2970.

42. Wang, A.; Wang, H.; Liu, Y.; Zhao, M.; Zhang, H.; Lu, Z.; Fang, Y.; Chen, X.; Liu, G. The prognostic value of PD-L1 expression for non-small cell lung cancer patients: a meta-analysis. Eur. J. Surg. Oncol. (Ejso) 2015, 41, 450–456.

43. Muenst, S.; Schaerli, A.; Gao, F.; Däster, S.; Trella, E.; Droeser, R.; Muraro, M.; Zajac, P.; Zanetti, R.; Gillanders, W. Expression of programmed death ligand 1 (PD-L1) is associated with poor prognosis in human breast cancer. Breast Cancer Res. Treat. 2014, 146, 15–24.

44. Kuang, D.-M.; Zhao, Q.; Peng, C.; Xu, J.; Zhang, J.-P.; Wu, C.; Zheng, L. Activated monocytes in peritumoral stroma of hepatocellular carcinoma foster immune privilege and disease progression through PD-L1. J. Exp. Med. 2009, 206, 1327–1337.

45. Topalian, S.L.; Drake, C.G.; Pardoll, D.M. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 2015, 27, 450–461.

46. Curiel, T.J.; Coukos, G.; Zou, L.; Alvarez, X.; Cheng, P.; Mottram, P.; Evdemon-Hogan, M.; Conejo-Garcia, J.R.; Zhang, L.; Burow, M. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat. Med. 2004, 10, 942–949.

47. Han, Y.; Yang, Y.; Chen, Z.; Jiang, Z.; Gu, Y.; Liu, Y.; Xu, S.; Lin, C.; Pan, Z.; Zhou, W. Human hepatocellular carcinoma-infiltrating CD4+ CD69+ Foxp3− regulatory T cell suppresses T cell response via membrane-bound TGF-β1. J. Mol. Med. 2014, 92, 539–550.

48. Borghaei, H.; Paz-Ares, L.; Horn, L.; Spigel, D.R.; Steins, M.; Ready, N.E.; Chow, L.Q.; Vokes, E.E.; Felip, E.; Holgado, E. Nivolumab versus docetaxel in advanced nonsquamous non–small-cell lung cancer. New Engl. J. Med. 2015, 373, 1627–1639.

49. Garon, E.B.; Rizvi, N.A.; Hui, R.; Leighl, N.; Balmanoukian, A.S.; Eder, J.P.; Patnaik, A.; Aggarwal, C.; Gubens, M.; Horn, L. Pembrolizumab for the treatment of non–small-cell lung cancer. New Engl. J. Med. 2015, 372, 2018–2028.

50. Hodi, F.S.; O'Day, S.J.; McDermott, D.F.; Weber, R.W.; Sosman, J.A.; Haanen, J.B.; Gonzalez, R.; Robert, C.; Schadendorf, D.; Hassel, J.C. Improved survival with ipilimumab in patients with metastatic melanoma. New Engl. J. Med. 2010, 363, 711–723.

51. Larkin, J.; Chiarion-Sileni, V.; Gonzalez, R.; Grob, J.J.; Cowey, C.L.; Lao, C.D.; Schadendorf, D.; Dummer, R.; Smylie, M.; Rutkowski, P. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. New Engl. J. Med. 2015, 373, 23–34.

52. Schadendorf, D.; Hodi, F.S.; Robert, C.; Weber, J.S.; Margolin, K.; Hamid, O.; Patt, D.; Chen, T.-T.; Berman, D.M.; Wolchok, J.D. Pooled analysis of long-term survival data from phase II and phase III trials of ipilimumab in unresectable or metastatic melanoma. J. Clin. Oncol. 2015, 33, 1889.

53. Robert, C.; Thomas, L.; Bondarenko, I.; O'Day, S.; Weber, J.; Garbe, C.; Lebbe, C.; Baurain, J.-F.; Testori, A.; Grob, J.-J. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. New Engl. J. Med. 2011, 364, 2517–2526.

54. Jenkins, R.W.; Barbie, D.A.; Flaherty, K.T. Mechanisms of resistance to immune checkpoint inhibitors. Br. J. Cancer 2018, 118, 9–16.

55. Darvin, P.; Toor, S.M.; Nair, V.S.; Elkord, E. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp. Mol. Med. 2018, 50, 1–11.