B7 Family

Subjects: Biology

Contributor: Noora Karim Ahangar

B7 family members, as immune checkpoint molecules, can substantially regulate immune responses. Since microRNAs (miRs) can regulate gene expression post-transcriptionally, we conducted a scoping review to summarize and discuss the regulatory cross-talk between miRs and new B7 family immune checkpoint molecules, i.e., B7-H3, B7-H4, B7-H5, butyrophilin like 2 (BTNL2), B7-H6, B7-H7, and immunoglobulin like domain containing receptor 2 (ILDR2).

B7 microRNA human diseases cancer immune checkpoint immunotherapy gene therapy

1. Introduction

Immune checkpoints can considerably regulate immune responses [1]. These molecules are critical for maintaining self-tolerance and preventing the stimulation of immune responses against normal peripheral tissues. Indeed, suppressing inhibitory axes, e.g., the immune checkpoint axis of cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed death-ligand 1 (PD-L1), has revolutionized cancer immunotherapy [2].

The B7 family is a group of immune checkpoints commonly expressed in different immune cells, such as antigen-presenting cells, T cells, B cells, natural killer cells, and various tissues. They play a crucial role in immune response; for example, they have substantial roles in directing the fate of T cells by binding their receptors. Various members of the B7 family have been identified, e.g., *B7.1* (*CD80*), *B7.2* (*CD86*), *B7-H1* (*PD-L1*, or *CD274*), *B7-DC* (*PD-L2*, *PDC1LG2*, or *CD273*), *B7-H2* (*ICOSL*: inducible T-cell co-stimulator ligand, or *CD275*), *B7-H3* (*CD276*), *B7-H4* (*VTCN1*), *B7-H5* (*VISTA*: V-domain Ig suppressor of T cell activation, *Dies1*: differentiation of embryonic stem cells 1, or *C10orf54*), butyrophilin like 2 (*BTNL2*), *B7-H6* (*NCR3LG1*: natural killer cell cytotoxicity receptor 3 ligand 1), *B7-H7* (*HHLA2*: human endogenous retro virus–H long repeat-associating 2), and immunoglobulin like domain containing receptor 2 (*ILDR2*) [2][3][4][5][6]. Indeed, BTNL2 and ILDR2 are introduced as B7-like molecules, and further investigation is needed. B7 family genes have been linked with various pathological conditions, e.g., cancers, infections, autoimmune diseases, and transplantation complications [6]. Thus, a better understanding of their biology might pave the way for introducing novel strategies to treat the abovementioned diseases and complications.

MicroRNAs (miRs), as small, non-coding RNAs, can bind to their complementary sequences, which are often the mRNA 3′-untranslated regions (3′UTR) of their targets. Since miRs can cleave their target mRNAs by guiding the

RNA-induced silencing complex (RISC) to target mRNAs, in order to direct the cleavage of mRNA through Argonaute (AGO) endonuclease activity [7], destabilize their target mRNAs via cutting their poly(A) tail, and make the translation of their target mRNA less effective, they are considered potent post-transcriptional gene regulators [8][9][10]. In higher eukaryotes, miRs can regulate the expression of approximately 60% of genes. It is well-established that miRs can contribute to many biological processes, e.g., cell growth, differentiation, metabolism, and immune response regulation [11][12]. Indeed, miRs can modulate the function of immune cells and regulate the expression of immune checkpoints [13][14][15]. Thus, alteration in miR expression is involved in the pathogenesis of various human diseases, like cancers [11][13][16]. Moreover, miRs can regulate the expression of B7 family members in various diseases; thus, there is a need to properly understand the scope and effect of this regulation in human diseases [17][18].

2. The Regulatory Cross-Talk between microRNAs and Novel Members of the B7 Family in Human Diseases

2.1. B7-H3

B7–H3, also referred to as *CD276*, can regulate the stimulation and inhibition of T cells [19][20]. A variety of cells, e.g., natural killer cells, activated T-cells, dendritic cells, macrophages, and non-hematopoietic cells, can express *B7-H3* [21]. Preliminary findings reported that B7-H3 could promote CD4+ and CD8+ T cell proliferation by T cell receptor (TCR) stimulation using immobilized Ig fusion protein [19]. However, it is well-established that B7–H3 can suppress the activation of CD4+ T-cell and the release of effector cytokines [22][23]. This suppression might facilitate the function of transcription factors like nuclear factor of activated T cells (NF-AT), nuclear factor kappa B (NF-κB), and activator protein 1 (AP-1), playing significant roles in T cell function [22]. Moreover, *B7-H3* overexpression has been identified in various cancers, e.g., breast [24], lung [25], kidney, prostate [26], and ovarian cancer [27]. Furthermore, the inhibition of *B7-H3* has decreased angiogenesis in medulloblastoma, indicating its essential role in tumor angiogenesis [28]. As an overexpressed oncogene in various cancers, MYC has a critical role in cancer development, e.g., angiogenesis, apoptosis, proliferation [29][30]. Since MYC inhibition has been associated with the suppressed expression of *B7-H3* in medulloblastoma cells, the MYC-*B7-H3* regulatory axis can play an essential role in regulating angiogenesis [28]. It has been indicated that *B7-H3* knockdown can repress the PI3K/Akt pathway, resulting in decreased STAT3 activity. Since STAT3 can promote the expression of matrix metalloproteinase 2 (*MMP2*) and matrix metalloproteinase 9 (*MMP9*), B7-H3 can regulate the expression of *MMP2* and *MMP9* [31]. Moreover, *B7-H3* can be involved in inflammatory conditions, e.g., sepsis and bacterial meningitis [32]. Since the mRNA expression of *B7–H3* is not as remarkable as its protein expression, the post-transcriptional regulating process might have a considerable effect [21].

2.2. B7-H4

B7-H4, also known as *B7x*, *B7S1*, and *VTCN1*, can inhibit cytokine production, proliferation, cell cycle progression, and the stimulation of $CD4^+$ and $CD8^+$ T cells [33][34]. Although its transcripts can be found in various tissues, its protein has low expression in most human normal tissues [35]. *B7-H4* expression is positively correlated with cancer

development in patients with gastric cancer [36], glioma [37], squamous cell esophageal carcinoma [38], renal cell carcinoma [39], pancreatic cancer [40], cholangiocarcinoma [18], ovarian cancer [41], and lung cancer [42]. Since *B7-H4* has been associated with cancer development, it can be an appealing target for treating cancer patients [35].

It has been shown that miR-125b-5p has an anti-inflammatory role and can regulate interleukin (IL)-1β-induced inflammatory genes by targeting the TNF receptor associated factor (TRAF6)/mitogen-activated protein kinase (MAPK)/NF-κB pathway in human osteoarthritic chondrocytes [43]. However, miR-125b-5p overexpression in macrophages can increase IL-2 secretion and the proliferation of $CD8^+$ T cells. Indeed, miR-125b-5p can target *B7-H4* and facilitate inflammation [44]. In line with this, *B7-H4* overexpression has been associated with poor prognosis in colorectal cancer patients [45]. In 24.4% of colorectal cancer patients, single-nucleotide polymorphism (SNP) rs13505 GG of *B7-H4* can confer an alternate binding site for miR-1207–5p, which might result in downregulation of this gene [46]. Furthermore, TGF-β1 can upregulate *B7-H4* and facilitate immune escape via the miR-155/miR-143 axis in colorectal cancer [47].

In 2017, 62 hsa-miRs were identified as regulating *B7-H4* in pancreatic cancer [48]. These miRs were mentioned above in the Results section.

2.3. B7-H5

B7-H5, also known as VISTA, C10orf54, Dies1, and PD-1H, is a type-I membrane protein that can stimulate terminal differentiation of embryonic stem cells (ESCs) into cardiomyocytes/neurons via the bone morphogenetic protein (BMP) signaling pathway [49]. It has been reported that miR-125a-5p can directly repress the transcription of *B7-H5* and inhibit ESC differentiation [50]. B7-H5 also plays a pivotal regulatory function in adipocyte differentiation independently from BMP signaling. In particular, the elevated level of *B7-H5* has been shown exclusively in differentiated fat cells and blocked adipocyte differentiation [51]. In *B7-H5* knockout mice, the elevation of inflammatory cytokines can result in chronic multi-organ inflammation, indicating the critical role of B7-H5 in suppressing inflammation [52]. In Crohn's disease, there is a negative association between *B7-H5* expression and hsa-miR-16–1 [53]. B7-H5 can serve as a ligand and receptor on T cells, suppressing the activation of naïve and memory T cells [54][55]. The presence of two PKC binding sites in the cytoplasmic region of B7-H5 might indicate that B7-H5 is a receptor [56][57]. *B7-H5* can be overexpressed in cancer-associated/cancer-adjacent gastric myofibroblasts. However, *B7-H5* expression is generally downregulated in epithelial gastric cancer cells. This can be explained by *B7-H5* promoter methylation, the overexpression of miR-125a-5p, or a combination of both, and even the existence of mutant *p53* [58]. Indeed, the downregulation of *B7-H5* has been associated with de-differentiation and triggered epithelial–mesenchymal transition (EMT) in epithelial cells.

2.4. B7-H6

B7-H6, also known as NCR3LG1, is a ligand for the NKp30 [59]. B7-H6 sequence is functionally similar to the other B7 family members. Although *B7-H6* is not found in normal human tissues, it is highly expressed in cancers, e.g., renal cell carcinoma, leukemia, breast cancer, ovarian cancer, and sarcomas [60]. Various factors can regulate *B7-H6* expressions, e.g., protease inhibitors, proinflammatory cytokines, natural killer cells, and miRs. Histone

deacetylase inhibitors (HDACi) and metalloprotease inhibitors can regulate the *B7-H6* expression at transcription and post-transcriptional levels, respectively [61]. Following stimulation of $CD14^+CD16^+$ neutrophils and monocytes, B7-H6 can be expressed on these proinflammatory immune cells [62]. Tumoral B7-H6 can be recognized and eliminated via natural killer cells. However, metalloproteases can cleave B7-H6 and shield tumor cells from natural killer-mediated immune responses [63]. Bioinformatics analysis has predicted that miR-93, miR-195, and miR-340 can regulate immune responses by targeting *B7-H6* in breast cancer cells [64].

2.5. B7-H7

B7-H7, which has previously been referred to as *B7-H5*, is known as the human endogenous retro virus–H long repeat-associating 2 (*HHLA2*) [65][66]. Its receptors can be found on various immune cells, e.g., monocytes, T cells, B cells, and dendritic cells. TMIGD2, which is referred to as CD28 homolog, is one of the identified B7-H7 receptors [67]. In antigen-presenting cells, B7-H7 co-stimulates the proliferation of naïve T cell and cytokine production across TMIGD2 by serine–threonine kinase AKT phosphorylation. However, the second B7-H7 receptor on activated T cells can exert a coinhibitory role, because activated T cells do not express TMIGD2. The identification of the second receptor might clarify the role of B7-H7 in T cell activation and the tumor microenvironment [68]. It has been reported that *B7-H7* is upregulated in lung cancer, osteosarcoma, and breast cancer, and its elevated expression is correlated with a poor prognosis in affected patients [69]. BATF in B lymphocytes and SMAD in monocytes might be involved in the dysregulation of *B7-H7* in kidney clear-cell carcinoma. It has been indicated that hsa-miR-6870–5p and hsa-miR-3116 might have a role in this modulatory mechanism [70].

2.6. Bioinformatics Analysis

Based on our results, four potential new interactions between B7 family members and miRs have been identified: (1) the hsa-miR-29b-3p/*B7-H3* axis, (2) the hsa-miR-29a-3p/*B7-H3* axis, (3) the hsa-miR-125a-5p/*B7-H4* axis, and (4) the hsa-miR-486-5p/*B7-H4* axis. Of these four interactions, the association of different isoforms of miR-29 with *B7-H3* has been investigated in previous studies (see above). As mentioned earlier, hsa-miR-125a-5p regulates *B7-H5* expression in gastric cancer, but its association with *B7-H4* has not been studied. Recent findings have shown that miR-125a-5p plays a pivotal role in suppressing the classical activation of macrophages (M1-type) induced by lipopolysaccharide (LPS) stimulation, while promoting IL-4-induced expression of the alternative M2 macrophages by targeting KLF13, a transcriptional factor that is involved in T lymphocyte activation and inflammation [71]. In addition, miR-486-5p is an immunomodulatory tumor suppressor miR that has been reported to have key roles in various oncological and non-oncological disorders [72]. Although our knowledge about the role of miR-125a-5p/*B7-H4* and miR-486-5p/*B7-H4* axes in the immune pathways and the pathogenesis of various diseases is still preliminary, our in silico analysis can pave the way for further investigations.

References

1. Huang, C.; Zhu, H.-X.; Yao, Y.; Bian, Z.-H.; Zheng, Y.-J.; Li, L.; Moutsopoulos, H.M.; Gershwin, M.E.; Lian, Z.-X. Immune checkpoint molecules. Possible future therapeutic implications in autoimmune diseases. J. Autoimmun. 2019, 104, 102333.
2. Ni, L.; Dong, C. New B7 Family Checkpoints in Human Cancers. Mol. Cancer Ther. 2017, 16, 1203–1211.
3. Collins, M.; Ling, V.; Carreno, B.M. The B7 family of immune-regulatory ligands. Genome Biol. 2005, 6, 223.
4. Zhao, Y.; Zheng, Q.; Jin, L. The Role of B7 Family Molecules in Maternal–Fetal Immunity. Front. Immunol. 2020, 11.
5. Chapoval, A.I.; Chapoval, S.P.; Shcherbakova, N.S.; Shcherbakov, D.N. Immune Checkpoints of the B7 Family. Part 2. Representatives of the B7 Family B7-H3, B7-H4, B7-H5, B7-H6, B7-H7, and ILDR2 and Their Receptors. Russ. J. Bioorgan. Chem. 2019, 45, 321–334.
6. Janakiram, M.; Shah, U.A.; Liu, W.; Zhao, A.; Schoenberg, M.P.; Zang, X. The third group of the B7-CD28 immune checkpoint family: HHLA2, TMIGD2, B7x, and B7-H3. Immunol. Rev. 2017, 276, 26–39.
7. Bartel, D.P. Metazoan MicroRNAs. Cell 2018, 173, 20–51.
8. Bartel, D.P. MicroRNAs: Genomics, biogenesis, mechanism, and function. Cell 2004, 116, 281–297.
9. Shirafkan, N.; Shomali, N.; Kazemi, T.; Shanehbandi, D.; Ghasabi, M.; Baghbani, E.; Ganji, M.; Khaze, V.; Mansoori, B.; Baradaran, B. microRNA-193a-5p inhibits migration of human HT-29 colon cancer cells via suppression of metastasis pathway. J. Cell. Biochem. 2018.
10. Bartel, D.P. MicroRNAs: Target recognition and regulatory functions. Cell 2009, 136, 215–233.
11. Christopher, A.F.; Kaur, R.P.; Kaur, G.; Kaur, A.; Gupta, V.; Bansal, P. MicroRNA therapeutics: Discovering novel targets and developing specific therapy. Perspect. Clin. Res. 2016, 7, 68–74.
12. Sadeghiyeh, N.; Sehati, N.; Mansoori, B.; Mohammadi, A.; Shanehbandi, D.; Khaze, V.; Baradaran, B. MicroRNA-145 replacement effect on growth and migration inhibition in lung cancer cell line. Biomed. Pharmacother. 2019, 111, 460–467.
13. Yang, Y.; Alderman, C.; Sehlaoui, A.; Xiao, Y.; Wang, W. MicroRNAs as Immunotherapy Targets for Treating Gastroenterological Cancers. Can. J. Gastroenterol. Hepatol. 2018, 2018, 9740357.
14. Argentiero, A.; De Summa, S.; Di Fonte, R.; Iacobazzi, R.M.; Porcelli, L.; Da Vià, M.; Brunetti, O.; Azzariti, A.; Silvestris, N.; Solimando, A.G. Gene Expression Comparison between the Lymph Node-Positive and -Negative Reveals a Peculiar Immune Microenvironment Signature and a Theranostic Role for WNT Targeting in Pancreatic Ductal Adenocarcinoma: A Pilot Study. Cancers 2019, 11, 942.

15. Porcelli, L.; Iacobazzi, R.M.; Di Fonte, R.; Serratì, S.; Intini, A.; Solimando, A.G.; Brunetti, O.; Calabrese, A.; Leonetti, F.; Azzariti, A.; et al. CAFs and TGF-β Signaling Activation by Mast Cells Contribute to Resistance to Gemcitabine/Nabpaclitaxel in Pancreatic Cancer. Cancers 2019, 11, 330.
16. Longo, V.; Brunetti, O.; Gnoni, A.; Cascinu, S.; Gasparini, G.; Lorusso, V.; Ribatti, D.; Silvestris, N. Angiogenesis in pancreatic ductal adenocarcinoma: A controversial issue. Oncotarget 2016, 7, 58649–58658.
17. Holla, S.; Stephen-Victor, E.; Prakhar, P.; Sharma, M.; Saha, C.; Udupa, V.; Kaveri, S.V.; Bayry, J.; Balaji, K.N. Mycobacteria-responsive sonic hedgehog signaling mediates programmed death-ligand 1- and prostaglandin E2-induced regulatory T cell expansion. Sci. Rep. 2016, 6, 24193.
18. Li, Z.; Wang, S.; Zhao, W.; Sun, Z.; Yan, H.; Zhu, J. Oxidized low-density lipoprotein upregulates microRNA-146a via JNK and NF-κB signaling. Mol. Med. Rep. 2016, 13, 1709–1716.
19. Chapoval, A.I.; Ni, J.; Lau, J.S.; Wilcox, R.A.; Flies, D.B.; Liu, D.; Dong, H.; Sica, G.L.; Zhu, G.; Tamada, K.; et al. B7-H3: A costimulatory molecule for T cell activation and IFN-gamma production. Nat. Immunol. 2001, 2, 269–274.
20. Leitner, J.; Klauser, C.; Pickl, W.F.; Stöckl, J.; Majdic, O.; Bardet, A.F.; Kreil, D.P.; Dong, C.; Yamazaki, T.; Zlabinger, G.; et al. B7-H3 is a potent inhibitor of human T-cell activation: No evidence for B7-H3 and TREML2 interaction. Eur. J. Immunol. 2009, 39, 1754–1764.
21. Veenstra, R.G.; Flynn, R.; Kreymborg, K.; McDonald-Hyman, C.; Saha, A.; Taylor, P.A.; Osborn, M.J.; Panoskaltsis-Mortari, A.; Schmitt-Graeff, A.; Lieberknecht, E.; et al. B7-H3 expression in donor T cells and host cells negatively regulates acute graft-versus-host disease lethality. Blood 2015, 125, 3335–3346.
22. Prasad, D.V.; Nguyen, T.; Li, Z.; Yang, Y.; Duong, J.; Wang, Y.; Dong, C. Murine B7-H3 is a negative regulator of T cells. J. Immunol. 2004, 173, 2500–2506.
23. Suh, W.K.; Gajewska, B.U.; Okada, H.; Gronski, M.A.; Bertram, E.M.; Dawicki, W.; Duncan, G.S.; Bukczynski, J.; Plyte, S.; Elia, A.; et al. The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses. Nat. Immunol. 2003, 4, 899–906.
24. Cong, F.; Yu, H.; Gao, X. Expression of CD24 and B7-H3 in breast cancer and the clinical significance. Oncol. Lett. 2017, 14, 7185–7190.
25. Sun, Y.; Wang, Y.; Zhao, J.; Gu, M.; Giscombe, R.; Lefvert, A.K.; Wang, X. B7-H3 and B7-H4 expression in non-small-cell lung cancer. Lung Cancer 2006, 53, 143–151.
26. Zang, X.; Thompson, R.H.; Al-Ahmadie, H.A.; Serio, A.M.; Reuter, V.E.; Eastham, J.A.; Scardino, P.T.; Sharma, P.; Allison, J.P. B7-H3 and B7x are highly expressed in human prostate cancer and associated with disease spread and poor outcome. Proc. Natl. Acad. Sci. USA 2007, 104, 19458–19463.

27. Fauci, J.M.; Straughn, J.M., Jr.; Ferrone, S.; Buchsbaum, D.J. A review of B7-H3 and B7-H4 immune molecules and their role in ovarian cancer. Gynecol. Oncol. 2012, 127, 420–425.
28. Purvis, I.J.; Avilala, J.; Guda, M.R.; Venkataraman, S.; Vibhakar, R.; Tsung, A.J.; Velpula, K.K.; Asuthkar, S. Role of MYC-miR-29-B7-H3 in Medulloblastoma Growth and Angiogenesis. J. Clin. Med. 2019, 8, 1158.
29. Chen, H.; Liu, H.; Qing, G. Targeting oncogenic Myc as a strategy for cancer treatment. Signal Transduct. Target. Ther. 2018, 3, 5.
30. Shchors, K.; Shchors, E.; Rostker, F.; Lawlor, E.R.; Brown-Swigart, L.; Evan, G.I. The Myc-dependent angiogenic switch in tumors is mediated by interleukin 1beta. Genes Dev. 2006, 20, 2527–2538.
31. Li, Y.; Guo, G.; Song, J.; Cai, Z.; Yang, J.; Chen, Z.; Wang, Y.; Huang, Y.; Gao, Q. B7-H3 Promotes the Migration and Invasion of Human Bladder Cancer Cells via the PI3K/Akt/STAT3 Signaling Pathway. J. Cancer 2017, 8, 816–824.
32. Zhang, X.; Zhao, X.; Sun, H.; Yan, Y.; Huang, L.; Gu, W.; Jiang, W.; Wang, Y.; Zhu, C.; Ji, W.; et al. The role of miR-29c/B7-H3 axis in children with allergic asthma. J. Transl. Med. 2018, 16, 218.
33. Prasad, D.V.; Richards, S.; Mai, X.M.; Dong, C. B7S1, a novel B7 family member that negatively regulates T cell activation. Immunity 2003, 18, 863–873.
34. Zang, X.; Loke, P.; Kim, J.; Murphy, K.; Waitz, R.; Allison, J.P. B7x: A widely expressed B7 family member that inhibits T cell activation. Proc. Natl. Acad. Sci. USA 2003, 100, 10388–10392.
35. MacGregor, H.L.; Ohashi, P.S. Molecular Pathways: Evaluating the Potential for B7-H4 as an Immunoregulatory Target. Clin. Cancer Res. 2017, 23, 2934–2941.
36. Cui, Y.; Li, Z. B7-H4 is Predictive of Poor Prognosis in Patients with Gastric Cancer. Med. Sci. Monit. 2016, 22, 4233–4237.
37. Yao, Y.; Ye, H.; Qi, Z.; Mo, L.; Yue, Q.; Baral, A.; Hoon, D.S.B.; Vera, J.C.; Heiss, J.D.; Chen, C.C.; et al. B7-H4(B7x)-Mediated Cross-talk between Glioma-Initiating Cells and Macrophages via the IL6/JAK/STAT3 Pathway Lead to Poor Prognosis in Glioma Patients. Clin. Cancer Res. 2016, 22, 2778–2790.
38. Wang, L.; Cao, N.N.; Wang, S.; Man, H.W.; Li, P.F.; Shan, B.E. Roles of coinhibitory molecules B7-H3 and B7-H4 in esophageal squamous cell carcinoma. Tumour Biol. 2016, 37, 2961–2971.
39. Krambeck, A.E.; Thompson, R.H.; Dong, H.; Lohse, C.M.; Park, E.S.; Kuntz, S.M.; Leibovich, B.C.; Blute, M.L.; Cheville, J.C.; Kwon, E.D. B7-H4 expression in renal cell carcinoma and tumor vasculature: Associations with cancer progression and survival. Proc. Natl. Acad. Sci. USA 2006, 103, 10391–10396.

40. Chen, X.; Tao, L.; Yuan, C.; Xiu, D. The prognostic value of B7-H4 in pancreatic cancer: Systematic review and meta-analysis. Medicine 2018, 97, e0088.
41. Liang, L.; Jiang, Y.; Chen, J.-S.; Niu, N.; Piao, J.; Ning, J.; Zu, Y.; Zhang, J.; Liu, J. B7-H4 expression in ovarian serous carcinoma: A study of 306 cases. Hum. Pathol. 2016, 57, 1–6.
42. Zhang, X.; Cai, L.; Zhang, G.; Shen, Y.; Huang, J. B7-H4 promotes tumor growth and metastatic progression in lung cancer by impacting cell proliferation and survival. Oncotarget 2017, 8, 18861–18871.
43. Rasheed, Z.; Rasheed, N.; Abdulmonem, W.A.; Khan, M.I. MicroRNA-125b-5p regulates IL-1β induced inflammatory genes via targeting TRAF6-mediated MAPKs and NF-κB signaling in human osteoarthritic chondrocytes. Sci. Rep. 2019, 9, 6882.
44. Diao, W.; Lu, L.; Li, S.; Chen, J.; Zen, K.; Li, L. MicroRNA-125b-5p modulates the inflammatory state of macrophages via targeting B7-H4. Biochem. Biophys. Res. Commun. 2017, 491, 912–918.
45. Liang, M.; Li, J.; Wang, D.; Li, S.; Sun, Y.; Sun, T.; Zhang, J.; Chen, X.; Li, Q.; Sun, S. T-cell infiltration and expressions of T lymphocyte co-inhibitory B7-H1 and B7-H4 molecules among colorectal cancer patients in northeast China’s Heilongjiang province. Tumor. Biol. 2014, 35, 55–60.
46. Wu, D.; Tang, R.; Qi, Q.; Zhou, X.; Zhou, H.; Mao, Y.; Li, R.; Liu, C.; Wang, W.; Hua, D.; et al. Five functional polymorphisms of B7/CD28 co-signaling molecules alter susceptibility to colorectal cancer. Cell. Immunol. 2015, 293, 41–48.
47. Zhou, X.; Mao, Y.; Zhu, J.; Meng, F.; Chen, Q.; Tao, L.; Li, R.; Fu, F.; Liu, C.; Hu, Y.; et al. TGF-β1 promotes colorectal cancer immune escape by elevating B7-H3 and B7-H4 via the miR-155/miR-143 axis. Oncotarget 2016, 7, 67196–67211.
48. Qian, Y.; Feng, L.; Wu, W.; Weng, T.; Hu, C.; Hong, B.; Wang, F.X.C.; Shen, L.; Wang, Q.; Jin, X.; et al. MicroRNA Expression Profiling of Pancreatic Cancer Cell Line L3.6p1 Following B7-H4 Knockdown. Cell. Physiol. Biochem. 2017, 44, 494–504.
49. Aloia, L.; Parisi, S.; Fusco, L.; Pastore, L.; Russo, T. Differentiation of embryonic stem cells 1 (Dies1) is a component of bone morphogenetic protein 4 (BMP4) signaling pathway required for proper differentiation of mouse embryonic stem cells. J. Biol. Chem. 2010, 285, 7776–7783.
50. Battista, M.; Musto, A.; Navarra, A.; Minopoli, G.; Russo, T.; Parisi, S. miR-125b regulates the early steps of ESC differentiation through dies1 in a TGF-independent manner. Int. J. Mol. Sci. 2013, 14, 13482–13496.
51. Ren, G.; Beech, C.; Smas, C.M. The immunoglobulin superfamily protein differentiation of embryonic stem cells 1 (dies1) has a regulatory role in preadipocyte to adipocyte conversion. PLoS ONE 2013, 8, e65531.

52. Wang, L.; Le Mercier, I.; Putra, J.; Chen, W.; Liu, J.; Schenk, A.D.; Nowak, E.C.; Suriawinata, A.A.; Li, J.; Noelle, R.J. Disruption of the immune-checkpoint VISTA gene imparts a proinflammatory phenotype with predisposition to the development of autoimmunity. Proc. Natl. Acad. Sci. USA 2014, 111, 14846–14851.
53. Wu, L.Y.; Ma, X.P.; Shi, Y.; Bao, C.H.; Jin, X.M.; Lu, Y.; Zhao, J.M.; Zhou, C.L.; Chen, D.; Liu, H.R. Alterations in microRNA expression profiles in inflamed and noninflamed ascending colon mucosae of patients with active Crohn's disease. J. Gastroenterol. Hepatol. 2017, 32, 1706–1715.
54. Lines, J.L.; Pantazi, E.; Mak, J.; Sempere, L.F.; Wang, L.; O'Connell, S.; Ceeraz, S.; Suriawinata, A.A.; Yan, S.; Ernstoff, M.S.; et al. VISTA is an immune checkpoint molecule for human T cells. Cancer Res. 2014, 74, 1924–1932.
55. Wang, L.; Rubinstein, R.; Lines, J.L.; Wasiuk, A.; Ahonen, C.; Guo, Y.; Lu, L.F.; Gondek, D.; Wang, Y.; Fava, R.A.; et al. VISTA, a novel mouse Ig superfamily ligand that negatively regulates T cell responses. J. Exp. Med. 2011, 208, 577–592.
56. Flies, D.B.; Han, X.; Higuchi, T.; Zheng, L.; Sun, J.; Ye, J.J.; Chen, L. Coinhibitory receptor PD-1H preferentially suppresses CD4+ T cell-mediated immunity. J. Clin. Investig. 2014, 124, 1966–1975.
57. Ohno, T.; Zhang, C.; Kondo, Y.; Kang, S.; Furusawa, E.; Tsuchiya, K.; Miyazaki, Y.; Azuma, M. The immune checkpoint molecule VISTA regulates allergen-specific Th2-mediated immune responses. Int. Immunol. 2018, 30, 3–11.
58. Oliveira, P.; Carvalho, J.; Rocha, S.; Azevedo, M.; Reis, I.; Camilo, V.; Sousa, B.; Valente, S.; Paredes, J.; Almeida, R.; et al. Dies1/VISTA expression loss is a recurrent event in gastric cancer due to epigenetic regulation. Sci. Rep. 2016, 6, 34860.
59. Flajnik, M.F.; Tlapakova, T.; Criscitiello, M.F.; Krylov, V.; Ohta, Y. Evolution of the B7 family: Co-evolution of B7H6 and NKp30, identification of a new B7 family member, B7H7, and of B7's historical relationship with the MHC. Immunogenetics 2012, 64, 571–590.
60. Brandt, C.S.; Baratin, M.; Yi, E.C.; Kennedy, J.; Gao, Z.; Fox, B.; Haldeman, B.; Ostrander, C.D.; Kaifu, T.; Chabannon, C.; et al. The B7 family member B7-H6 is a tumor cell ligand for the activating natural killer cell receptor NKp30 in humans. J. Exp. Med. 2009, 206, 1495–1503.
61. Chen, Y.; Mo, J.; Jia, X.; He, Y. The B7 Family Member B7-H6: A New Bane of Tumor. Pathol. Oncol. Res. 2018, 24, 717–721.
62. Matta, J.; Baratin, M.; Chiche, L.; Forel, J.M.; Cognet, C.; Thomas, G.; Farnarier, C.; Piperoglou, C.; Papazian, L.; Chaussabel, D.; et al. Induction of B7-H6, a ligand for the natural killer cell-activating receptor NKp30, in inflammatory conditions. Blood 2013, 122, 394–404.
63. Schlecker, E.; Fiegler, N.; Arnold, A.; Altevogt, P.; Rose-John, S.; Moldenhauer, G.; Sucker, A.; Paschen, A.; von Strandmann, E.P.; Textor, S.; et al. Metalloprotease-mediated tumor cell

shedding of B7-H6, the ligand of the natural killer cell-activating receptor NKp30. Cancer Res. 2014, 74, 3429–3440.

64. Yang, L.; Cai, Y.; Zhang, D.; Sun, J.; Xu, C.; Zhao, W.; Jiang, W.; Pan, C. miR-195/miR-497 Regulate CD274 Expression of Immune Regulatory Ligands in Triple-Negative Breast Cancer. J. Breast Cancer 2018, 21, 371–381.
65. Wang, C.; Feng, H.; Cheng, X.; Liu, K.; Cai, D.; Zhao, R. Potential Therapeutic Targets of B7 Family in Colorectal Cancer. Front. Immunol. 2020, 11.
66. Zhu, Y.; Yao, S.; Iliopoulou, B.P.; Han, X.; Augustine, M.M.; Xu, H.; Phennicie, R.T.; Flies, S.J.; Broadwater, M.; Ruff, W.; et al. B7-H5 costimulates human T cells via CD28H. Nat. Commun. 2013, 4, 2043.
67. Janakiram, M.; Chinai, J.M.; Zhao, A.; Sparano, J.A.; Zang, X. HHLA2 and TMIGD2: New immunotherapeutic targets of the B7 and CD28 families. Oncoimmunology 2015, 4, e1026534.
68. Xiao, Y.; Freeman, G.J. A New B7:CD28 Family Checkpoint Target for Cancer Immunotherapy: HHLA2. Clin. Cancer Res. 2015, 21, 2201–2203.
69. Rieder, S.A.; Wang, J.; White, N.; Qadri, A.; Menard, C.; Stephens, G.; Karnell, J.L.; Rudd, C.E.; Kolbeck, R. B7-H7 (HHLA2) inhibits T-cell activation and proliferation in the presence of TCR and CD28 signaling. Cell. Mol. Immunol. 2020.
70. Wang, B.; Ran, Z.; Liu, M.; Ou, Y. Prognostic Significance of Potential Immune Checkpoint Member HHLA2 in Human Tumors: A Comprehensive Analysis. Front. Immunol. 2019, 10, 1573.
71. Banerjee, S.; Cui, H.; Xie, N.; Tan, Z.; Yang, S.; Icyuz, M.; Thannickal, V.J.; Abraham, E.; Liu, G. miR-125a-5p regulates differential activation of macrophages and inflammation. J. Biol. Chem. 2013, 288, 35428–35436.
72. ElKhouly, A.M.; Youness, R.A.; Gad, M.Z. MicroRNA-486-5p and microRNA-486-3p: Multifaceted pleiotropic mediators in oncological and non-oncological conditions. Non-Coding RNA Res. 2020, 5, 11–21.