Cellular Immunology 346 (2019) 103957

Contents lists available at ScienceDirect

Cellular Immunology

journal homepage: www.elsevier.com/locate/ycimm

Signalling molecules and epigenetic targeting in cancer immunotherapy – Comments on "Epigenetic modulation enhances immunotherapy for hepatocellular carcinoma"

The immune system plays a key role in cancer initiation, progression and therapy. Dysregulation of immune responses has been reported as a hallmark of cancer development [1]. Therefore, reactivation of tactical immune responses against cancers is of great importance in cancer immunotherapy. Indeed, cancer immunotherapy has been well recognized to increase survival rate of several types of cancers which have high mutation rates and neoantigen expression. For example, anti-Programmed Death-Ligand 1/anti-Programmed Cell Death Protein 1 (anti-PD-L1/anti-PD-1) have importantly improved therapeutic outcomes in a proportion of patients diagnosed with melanoma, kidney cancer and non-small cell lung cancer [1]. However, the response rate to immunotherapy in hepatocellular carcinoma (HCC) is low due to the underexpression of cancer neoantigens [2].

The study by Hong et al. (2019) showed that inhibition of epigenetic molecules DNA methyltransferase 1 (DNMT1) and enhancer of zeste homolog 2 (EZH2) increased efficacy of immunotherapy in HCC. The mechanisms were revealed to be increasing cytotoxic T-cells trafficking to the site of the tumour mediated by increased expression of CXCL9 and CXCL10 and inducing previously silent neoantigens such as cancer testis antigens NY-ESO-1 (New York esophageal squamous cell carcinoma 1) and LAGE (L antigen family member 1), facilitating immune targets against the cancer cells [3]. In a mouse model, epigenetic modulation of DNMT1 and EZH2 increased the treatment efficacy of anti-PD-L1, resulting in tumour regression. The investigation opens a novel pathway for the treatment of cancers with low cancer antigenicity. Mechanistically, it can be well incorporated into the signalling regulation of PD-L1 and cancer neoantigen expression (Fig. 1).

PD-L1 expression is regulated by both genetic and epigenetic factors. Major signalling molecules including Akt, Stat3, NF-κB, Erk and HIF-1 have been demonstrated to regulate PD-L1 expression [1]. Epigenetically, miRNA-513 and miRNA-570 can regulate PD-L1 mRNA stability [1]. Of significant interest is that PD-L1 can also stimulate Akt activity and thus form a feed-forward loop. The study by Hong and colleagues (2019) demonstrated the importance of epigenetic molecules EZH2 and DNMT1 in the expression of cancer neoantigens and major histocompatibility complex (MHC). Both molecules are known to be regulated by signalling molecules such as Akt, Stat3, Erk and NF-κB [4,5]. Stat3 regulates EZH2 through long non-coding RNA HOTAIR [6]. Therefore, activation of these signalling molecules represses the expression of cancer neoantigens and MHC, which are necessary prompts for evoking anti-cancer immunity.

Epigenetic molecules such as butyrate may also have the capacity to regulate the expression of cancer neoantigens and MHC. This posit is commensurate with several studies demonstrated in *in vitro* cancer cells and animal models of cancer. The health benefits that have been attributed to the intestinal microbiome in part are due to the microbiota-synthesized short chain fatty acids (SCFAs) that encompass acetate, propionate and butyrate [7]. Recently several important studies have reported that the intestinal microbiota has a close association with cancer immunotherapy efficacy [8–12]. This could be mediated by butyrate, a SCFA signalling molecule reported to exhibit effects on multiple signalling pathways [7]. Furthermore, butyrate is known to inhibit histone deacetylases (HDACs), resulting in inhibition of multiple oncogenic signalling pathways [13]. Inhibition of HDACs has been shown to increase MHC expression [14]. Butyrate can also inhibit oncogenic pathways via HDAC-independent pathways. However, whether butyrate regulates PD-L1 is not well understood as yet; on current evidence [9] though, the posit has strong biological plausibility.

Overall, cancer immunotherapy shows wide promise and the further successful application of immunotherapy necessitates both infiltration of CTLs into tumours and cancer neoantigen expression. Both genetic and epigenetic molecules are involved in CTL activation and cancer neoantigen expression. Incorporating modulation of epigenetic molecules such as EZH2 and DNMT1 to improve immunotherapy could be an effective approach. Butyrate could also improve cancer immunotherapy through both signalling and epigenetic modulation and is warranted for further study.

DOI of original article: https://doi.org/10.1016/j.cellimm.2018.12.010

https://doi.org/10.1016/j.cellimm.2019.103957
Received 26 June 2019; Received in revised form 9 July 2019; Accepted 19 July 2019
Available online 18 October 2019

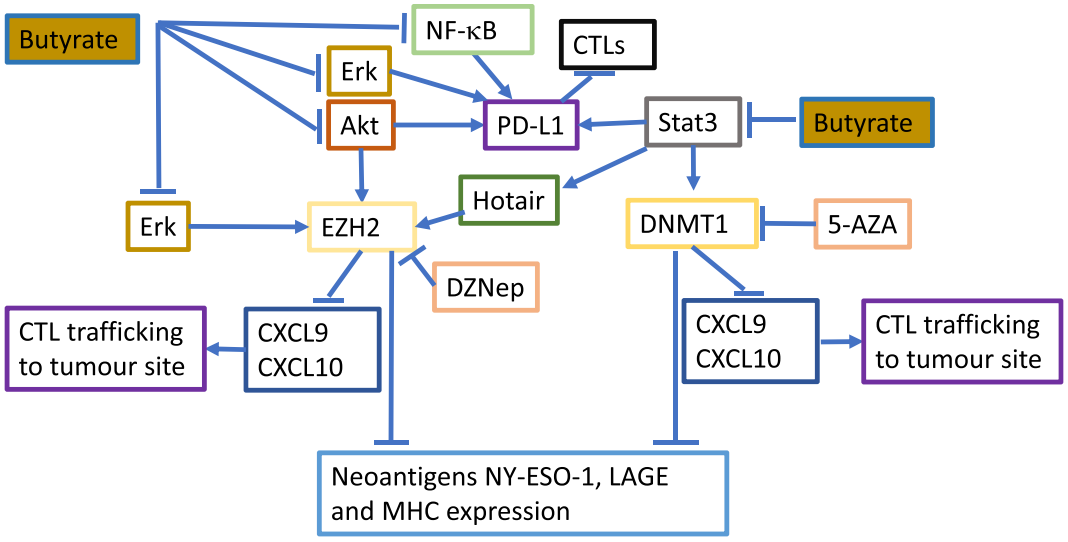

Fig. 1. The central roles of signalling molecules in the regulation of PD-L1 expression and cancer neoantigens. Signalling molecules Akt, Stat3, NF-κB and Erk can upregulate PD-L1 expression, which can block the activity of CTLs. Stat3 upregulates DNMT1 expression, leading to decreased expression of cancer neoantigens NY-ESO-1, LAGE and MHC. Akt and Erk upregulate EZH2 expression which also decreases expression of neoantigens. DNMT1 and EZH2 can block CXCL9 and CXCL10, resulting in decreased CTL trafficking to the tumour site. Stat3 also upregulates EZH2 via long non-coding RNA Hotair. Inhibition of DNMT1 by 5-Azacytidine and EZH2 by DZNep increases expression of neoantigens and CTL trafficking. *Abbreviations:* Akt, protein kinase B; CXCL9, C-X-C motif chemokine ligand 9; CXCL10, C-X-C motif chemokine ligand 10; CTLs, cytotoxic T lymphocytes; DNMT1, DNA methyltransferase 1; Erk, extracellular signal-regulated kinases; EZH2, enhancer of zeste homolog 2; LAGE, L antigen family member 1; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-light-chain-enhancer of activated B cells; NY-ESO-1, New York esophageal squamous cell carcinoma 1; Stat3, signal transducer and activator of transcription 3.

References

[1] J. Chen, C.C. Jiang, L. Jin, X.D. Zhang, Regulation of PD-L1: a novel role of pro-survival signalling in cancer, Ann. Oncol. 27 (3) (2016) 409–416.

[2] T.N. Schumacher, W. Scheper, P. Kvistborg, Cancer neoantigens, Annu. Rev. Immunol. 37 (2019) 173–200.

[3] Y.K. Hong, Y. Li, H. Pandit, S. Li, Z. Pulliam, Q. Zheng, Y. Yu, R.C.G. Martin, Epigenetic modulation enhances immunotherapy for hepatocellular carcinoma, Cell. Immunol. 336 (2019) 66–74.

[4] M. Yu, Y. Li, M. Li, D. Lu, Eudesmin exerts antitumor effects by down-regulating EZH2 expression in nasopharyngeal carcinoma cells, Chem. Biol. Interact. 307 (2019) 51–57.

[5] E. Riquelme, C. Behrens, H.Y. Lin, G. Simon, V. Papadimitrakopoulou, J. Izzo, C. Moran, N. Kalhor, J.J. Lee, J.D. Minna, Wistuba II, Modulation of EZH2 expression by MEK-ERK or PI3K-AKT signaling in lung cancer is dictated by different KRAS oncogene mutations, Cancer Res. 76 (3) (2016) 675–685.

[6] S. Sun, Y. Wu, W. Guo, F. Yu, L. Kong, Y. Ren, Y. Wang, X. Yao, C. Jing, C. Zhang, M. Liu, Y. Zhang, M. Zhao, Z. Li, C. Wu, Y. Qiao, J. Yang, X. Wang, L. Zhang, M. Li, X. Zhou, STAT3/HOTAIR signaling axis regulates HNSCC growth in an EZH2-dependent manner, Clin. Cancer Res. 24 (11) (2018) 2665–2677.

[7] J. Chen, K.N. Zhao, L. Vitetta, Effects of intestinal microbial elaborated butyrate on oncogenic signaling pathways, Nutrients 11 (5) (2019) 1026.

[8] V. Matson, J. Fessler, R. Bao, T. Chongsuwat, Y. Zha, M.L. Alegre, J.J. Luke, T.F. Gajewski, The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients, Science 359 (6371) (2018) 104–108.

[9] V. Gopalakrishnan, C.N. Spencer, L. Nezi, A. Reuben, M.C. Andrews, T.V. Karpinets, P.A. Prieto, D. Vicente, K. Hoffman, S.C. Wei, A.P. Cogdill, L. Zhao, C.W. Hudgens, D.S. Hutchinson, T. Manzo, M. Petaccia de Macedo, T. Cotechini, T. Kumar, W.S. Chen, S.M. Reddy, R. Szczepaniak Sloane, J. Galloway-Pena, H. Jiang, P.L. Chen, E.J. Shpall, K. Rezvani, A.M. Alousi, R.F. Chemaly, S. Shelburne, L.M. Vence, P.C. Okhuysen, V.B. Jensen, A.G. Swennes, F. McAllister, E. Marcelo Riquelme Sanchez, Y. Zhang, E. Le Chatelier, L. Zitvogel, N. Pons, J.L. Austin-Breneman, L.E. Haydu, E.M. Burton, J.M. Gardner, E. Sirmans, J. Hu, A.J. Lazar, T. Tsujikawa, A. Diab, H. Tawbi, I.C. Glitza, W.J. Hwu, S.P. Patel, S.E. Woodman, R.N. Amaria, M.A. Davies, J.E. Gershenwald, P. Hwu, J.E. Lee, J. Zhang, L.M. Coussens, Z.A. Cooper, P.A. Futreal, C.R. Daniel, N.J. Ajami, J.F. Petrosino, M.T. Tetzlaff, P. Sharma, J.P. Allison, R.R. Jenq, J.A. Wargo, Gut microbiome modulates response to anti-PD-1 immunotherapy in melanoma patients, Science 359 (6371) (2018) 97–103.

[10] V. Gopalakrishnan, B.A. Helmink, C.N. Spencer, A. Reuben, J.A. Wargo, The influence of the gut microbiome on cancer, immunity, and cancer immunotherapy, Cancer Cell 33 (4) (2018) 570–580.

[11] V. Gopalakrishnan, R.R. Jenq, Implicating or exonerating the gut microbiome in blood-borne infection, Nat. Med. 24 (12) (2018) 1788–1789.

[12] B. Routy, E. Le Chatelier, L. Derosa, C.P.M. Duong, M.T. Alou, R. Daillere, A. Fluckiger, M. Messaoudene, C. Rauber, M.P. Roberti, M. Fidelle, C. Flament, V. Poirier-Colame, P. Opolon, C. Klein, K. Iribarren, L. Mondragon, N. Jacquelot, B. Qu, G. Ferrere, C. Clemenson, L. Mezquita, J.R. Masip, C. Naltet, S. Brosseau, C. Kaderbhai, C. Richard, H. Rizvi, F. Levenez, N. Galleron, B. Quinquis, N. Pons, B. Ryffel, V. Minard-Colin, P. Gonin, J.C. Soria, E. Deutsch, Y. Loriot, F. Ghiringhelli, G. Zalcman, F. Goldwasser, B. Escudier, M.D. Hellmann, A. Eggermont, D. Raoult, L. Albiges, G. Kroemer, L. Zitvogel, Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors, Science 359 (6371) (2018) 91–97.

[13] X. Chang, H. Li, J. Feng, Y. Chen, G. Nie, J. Zhang, Effects of cadmium exposure on the composition and diversity of the intestinal microbial community of common carp (Cyprinus carpio L.), Ecotoxicol. Environ. Saf. 171 (2019) 92–98.

[14] Y. Komatsu, H. Hayashi, Histone deacetylase inhibitors up-regulate the expression of cell surface MHC class-I molecules in B16/BL6 cells, J. Antibiot. (Tokyo) 51 (1) (1998) 89–91.

Jiezhong Chen[a,*], Luis Vitetta[a,b,*]

[a] *Medlab Clinical Ltd, Sydney 2015, Australia*

[b] *The University of Sydney, Faculty of Medicine and Health, Sydney 2006, Australia*

E-mail addresses: Jiezhong_chen@medlab.co (J. Chen), luis.vitetta@sydney.edu.au, luis_vitetta@medlab.co (L. Vitetta).

[*] Corresponding authors at: Medlab Clinical Ltd, Sydney 2015, Australia.