International Journal of Research
Available at https://edupediapublications.org/journals
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 04 Issue-17
December 2017

Role of epigenetic modifications in inflammation and cancer

Mohd Ishaq Dar[1], Sameer Ahmad Mir[1], Parvaiz Ahmad Dar[2], Sameer Ahmad Khan[1], Aarif Ali [2], Mashooq Ahmad Dar[2].

[1] Cancer Pharmacology Division, IIIM, Jammu, Jammu and Kashmir.

[2] Department of Biochemistry, University of Kashmir, Jammu and Kashmir.

Email: darishaq1234@gmail.com

Abstract

Epigenetic modifications which include histone modifications acetylation and DNA methylation play an important role in expression of genes. Epigenetic modifications play an important role in development, progression of diseases like cancers and also have an important role in inflammation related disorders. In this review we will try to focus on different histone, DNA modifications and their role in inflammation and cancer. Cancer cells show immune tolerance by activation and inhibition of genes associated with inflammation and inflammatory response. A sort of peripheral immune tolerance is shown by cancer cells like our self antigens are recognised.

Keywords: Histone acetylation, DNA methylation, Histone methylation, inflammation.

Introduction

Regulation of gene expression occurs by epigenetic modification of histone tails by histone methyltransferases/demethylases, acetylation process by acetyltransferases/ histone deacetylases and DNA methylation by DNA methyltransferases [1]. Histone and DNA modifications play an important role in normal development as well as the progression of diseases like cancers and inflammation [2]. In early stages of cancer epigenetic modifications are altered which eventually initiate cancer development process [3, 4]. Most of the cancer cells are immune resistant because there is a downregulation in the expression of MHC genes as well as the expression of key inflammatory cytokines are silenced by epigenetic modifications [5, 6]. Various epidrugs like TSA, DNMT inhibitors are in clinical trials for reversing of immune tolerance in cancer cells [7] [8]. Reversal of immunological tolerance can be a possible can be a possible target for cancer prevention [9] [10]

International Journal of Research
Available at https://edupediapublications.org/journals
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 04 Issue-17
December 2017

Role of epigenetic modifications in cancer

Abbberant histone modifications are observed in various cancers in humans and various studies have shown that more than 300 genes are altered by epigenetic modifications of histones and DNA [4]. Hypermethylation of CpG islands in promoters of various tumour suppressors and DNA repair genes give growth advantage and cause genomic instability responsible for tumourigenicity [11, 12]. There is also a change in histone modification pattern in various tumours [13]. Histone modification suppress the expression of tumour suppressor genes by promoter methylation and induce the expression of oncogenes by modification having different histone methylation marks present in suppression [14] Figure 1

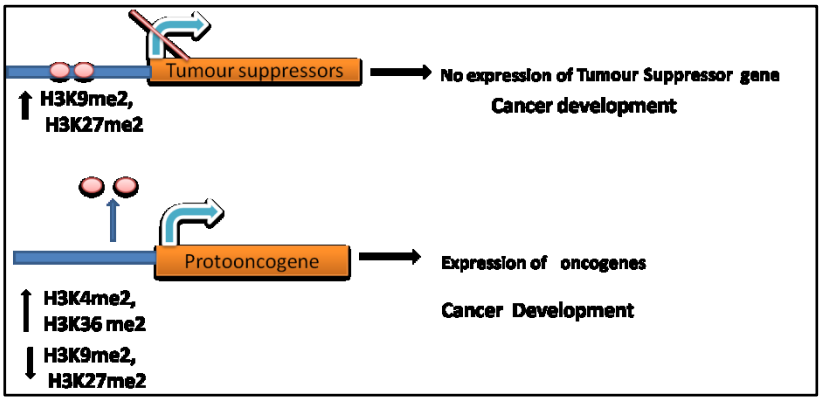

Figure 1. H3K9me2 and H3K27me2 cause transcriptional repression of tumour suppressor genes.H3K4me2 and H3K36me2 is responsible for transcriptional activation of oncogenes.

Role of epigenetics in inflammatory diseases

Various studies have shown that a global decrease in DNA methylation levels is observed in fibroblasts present in synovial joints of rheumatoid arthritis patients[14, 15]. Recent studies have shown that histone modification of TNF α Promoter is responsible for immunological tolerance in macrophages[16, 17] (Figure 2). Periodontitis is inflammatory disease caused due to decrease in expression of prostaglandin-endoperoxide synthase-2 gene expression due to hypermethylation of its promoter[18]. Promoter hypomethylation of Toll like receptor is associated with exaggerated immune response to bacterial endotoxins [19]. Increased histone acetyltransferase activity is associated with increased immune response while increase histone deacetylase activity is responsible for immune suppression [20].

International Journal of Research
Available at https://edupediapublications.org/journals
e-ISSN: 2348-6848
p-ISSN: 2348-795X
Volume 04 Issue-17
December 2017

Figure 2: H3K9me2 and H3K27me2 cause transcriptional TNF alpha responsible for immunological tolerance

Epigenetic changes and immune escape in cancer

Common hallmark of cancer is downregulation of immunity related genes which leads to reduced expression of proinflammatory genes and increased expression of anti-inflammatory genes and proteins [10]. Cancer cells escape immune response by epigenetic silencing of tumour suppressor genes [21]. Various studies have shown that in cancer cells there is a defect in presentation of antigens to immune cells or if the antigen is presented the interaction is weak [21]. Some studies are also proving that tumour antigens show immunological just like our self antigens are recognised [8]. Also research reports suggested that HDAC inhibitors augment immune response leading to cell death and apoptosis of cancer cells [8]. Some recent studies also reported that use of epidrugs can increase inflammatory response against tumour cells and help in elimination of tumours [10, 22] Figure 3.

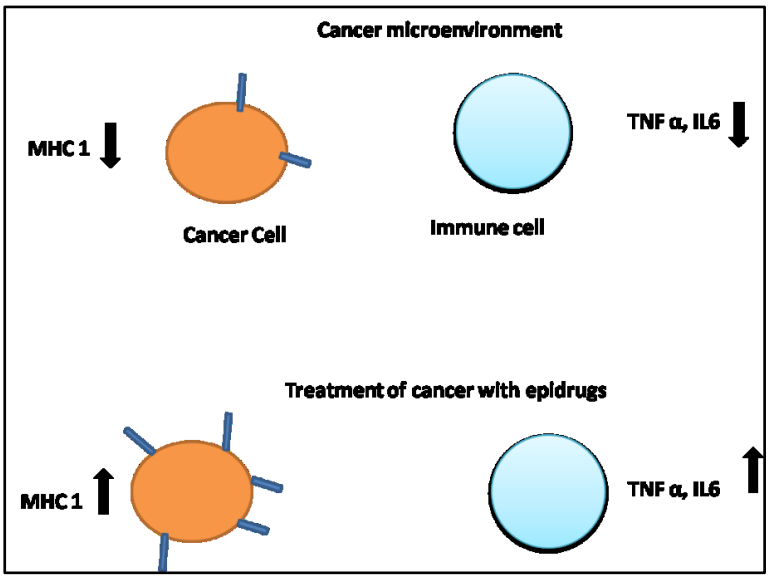

Figure 3. Reversal of immune tolerance

It has also been shown that HDAC inhibitor trichostatin A induce expression of MHC genes in tumour cells [21, 23]

Conclusion

Since histone methylation, acetylation and DNA methylation plays an important role in progression of diseases like cancer and inflammation related disorders. Current research and development all over the world is focussed on drugs targets these epigenetic pathways. In future more and new epigenetic drugs will emerge and help in targeting of diseases in an efficient manner.

References

1. Dawson, M.A. and T. Kouzarides, Cancer epigenetics: from mechanism to therapy. Cell. **150**(1): p. 12-27.
2. Bayarsaihan, D., Epigenetic mechanisms in inflammation. Journal of dental research. **90**(1): p. 9-17.
3. Banerjee, H.N. and M. Verma, Epigenetic mechanisms in cancer. Biomarkers in medicine, 2009. **3**(4): p. 397-410.
4. Kanwal, R. and S. Gupta, Epigenetic modifications in cancer. Clinical genetics. **81**(4): p. 303-311.
5. Leavy, O., New mechanism of tolerance induction in cancer. Nature Reviews Immunology, 2007. **7**(8): p. 580-580.
6. Vinay, D.S., et al. Immune evasion in cancer: Mechanistic basis and therapeutic strategies. in Seminars in cancer biology: Elsevier.
7. Chiappinelli, K.B., et al., Combining epigenetic and immunotherapy to combat cancer. Cancer research. **76**(7): p. 1683-1689.
8. Mazzone, R., et al., Epi-drugs in combination with immunotherapy: a new avenue to improve anticancer efficacy. Clinical Epigenetics. **9**(1): p. 59.
9. Mapara, M.Y. and M. Sykes, Tolerance and cancer: mechanisms of tumor evasion and strategies for breaking tolerance. Journal of Clinical Oncology, 2004. **22**(6): p. 1136-1151.
10. Hacninger, E., T.E.G. Krueger, and J.M. Lang, Augmenting antitumor immune responses with epigenetic modifying agents. Frontiers in immunology. **6**.
11. Sincic, N. and Z. Herceg, DNA methylation and cancer: ghosts and angels above the genes. Current opinion in oncology. **23**(1): p. 69-76.
12. Shen, L., et al., Genome-wide profiling of DNA methylation reveals a class of normally methylated CpG island promoters. PLoS genetics, 2007. **3**(10): p. e181.
13. Karli A, R., et al., Histone modification levels are predictive for gene expression. Proceedings of the National Academy of Sciences. **107**(7): p. 2926-2931.

14. Nelson, S., Comparative methylation hybridization. Nature Education, 2008. **1**(1): p. 55.

15. Karouzakis, E., et al., Epigenetic control in rheumatoid arthritis synovial fibroblasts. Nature Reviews Rheumatology, 2009. **5**(5): p. 266-272.

16. Lyroni, K., et al., Epigenetic and Transcriptional Regulation of IRAK-M Expression in Macrophages. The Journal of Immunology. **198**(3): p. 1297-1307.

17. El Gazzar, M., et al., G9a and HP1 couple histone and DNA methylation to TNFÎ± transcription silencing during endotoxin tolerance. Journal of Biological Chemistry, 2008. **283**(47): p. 32198-32208.

18. Zhang, S., et al., Alteration of PTGS2 promoter methylation in chronic periodontitis. Journal of dental research. **89**(2): p. 133-137.

19. Shuto, T., et al., Promoter hypomethylation of Toll-like receptor-2 gene is associated with increased proinflammatory response toward bacterial peptidoglycan in cystic fibrosis bronchial epithelial cells. The FASEB journal, 2006. **20**(6): p. 782-784.

20. Villagra, A., E.M. Sotomayor, and E. Seto, Histone deacetylases and the immunological network: implications in cancer and inflammation. Oncogene. **29**(2): p. 157-173.

21. Magner, W.J., et al., Activation of MHC class I, II, and CD40 gene expression by histone deacetylase inhibitors. The Journal of Immunology, 2000. **165**(12): p. 7017-7024.

22. Suarez -A□lvarez, B., et al., Epigenetic modulation of the immune function: a potential target for tolerance. Epigenetics. **8**(7): p. 694-702.

23. Tomasi, T.B., W.J. Magner, and A.N.H. Khan, Epigenetic regulation of immune escape genes in cancer. Cancer Immunology, Immunotherapy, 2006. **55**(10): p. 1159-1184.