International Journal of Advance Research in Science and Engineering
Volume No.06, Special Issue No.(03), December 2017
www.ijarse.com
IJARSE
ISSN: 2319-8354

Epigenetic modification and their role in normal development, regeneration, IPSC generation and disease progression

Mohd Ishaq Dar[1], Parvaiz Ahmad Dar[2], Khalid Bashir[3]

[1]CSIR IIIM Canal Road Jammu(India)

[2]Department of Biochemistry, University of Kashmir(India)

ABSTRACT

It has been thoroughly studied and proved that histone and DNA modifications are essential requirements for development processes, regeneration, pluoripotency and disease progression[1-3]. Various studies have shown that a global change in gene expression is associated with various developmental processes. Various enzymes like histone methyltransferases, acetyltransferases, histone demethylases and DNA methyltransferases are responsible for various epigenetic modifications and associated epigenetic changes [4]. Some of the epigenetic modifications are associated with gene silencing by formation of heterochromatin while some modification are associated with gene activation by formation of open active form euchromatin [5]. All epigenetic modifications are tightly regulated in cells [6].

Keywords: ***Regeneration, pluoripotency, methyltransferase, nacetyltranmsferase, heterochromatin and euchromatin***

I. INTRODUCTION

Epigenetic modifications are dynamic cellular proceeses essential for development and regeneration[7]. Epigenetic modification is tightly regulated and abberant epigenetic changes are responsible for many diseases in humans diseases[8].Various cellular enzymes are responsible for epigenetic changes and the related biological properties associated with them[9, 10]. Epigenetic modifications are responsible for silencing and activation of various genes(Figure 1)[11]. Histone acetylation of histones present in chromosomes open up chromosomes and the heterochromatin is converted into euchromatin and genes associated with them are activated[12]. While histone methylation are responsible for both activation and inhibition of genes[13]. Methylation H3K9me1/me2/me3, H3K27me1, me2, me3, H4K20me1, me2, me3 are responsible for gene inactivation while histone modifications H3K4me1/me2 and H3K36me1, me2 are responsible for gene activation[14, 15]. Epigenetic changes associated with DNA methylation play an important role in normal development processes in mammals as well as promoter hypermethylation in some diseases like cancer[16].

International Journal of Advance Research in Science and Engineering
Volume No.06, Special Issue No.(03), December 2017
www.ijarse.com
IJARSE
ISSN: 2319-8354

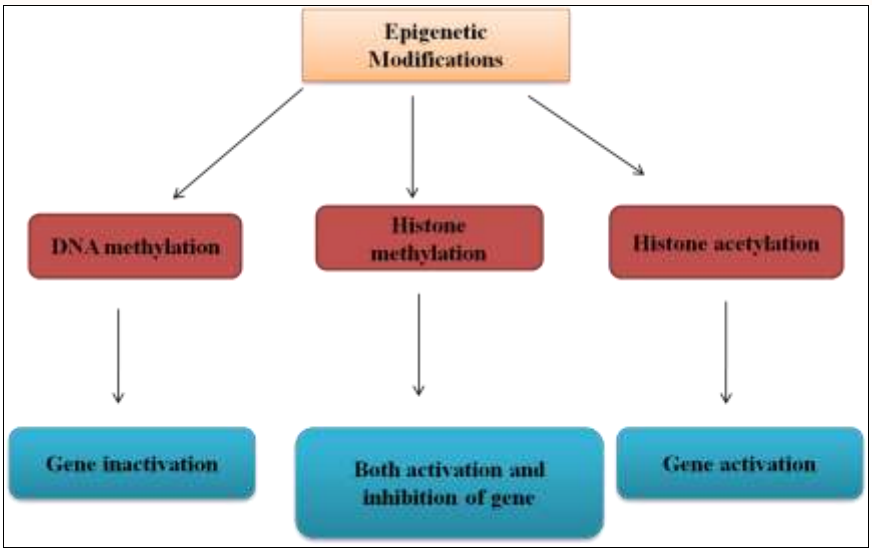

Figure 1: Epigenetic modifications associated with activation and inactivation of genes.

II. ROLE OF DNA METHYLATION IN NORMAL DEVELOPMENT, EPIGENETIC REPROGRAMMING AND CARCINOGENESIS

DNA methylation is an important guide for differentiation of cells during embryonic development into various lineages[17]. DNA methylation also represses the activation of retrotransposons and maintains genome integrity[17]. Hypermethylation of promoters of tumour suppressor genes which lead to their inactivation and cancer[18]. Studies have shown that DNA methylation of centromeric DNA is responsible for proper alignment of chromosomes during segregation[19].Various studies have shown that DNA methylation is very essential for genome imprinting and dosage compensation[17]. Also various research reports have shown that DNA hypermethylation is responsible for inactivation of pluoripotency genes OCT4 and SOX2 [20].

III. ROLE OF HISTONE METHYLATION IN NORMAL DEVELOPMENT, EPIGENETIC REPROGRAMMING AND CARCINOGENESIS

H3K9me3 and H3K27me3 methylation marks are downregulated in embryonic stages while as these methylation markers are upregulated in differentiated cells [21]. Studies in zebra fish have shown that H3K27me2 and H3K27 me3 methylation marks and histone demethylases are essential for caudal fin regeneration in zebra fish[22]. Various studies have shown that H3K9 me2 downregulation increase IPSC generation[23, 24]. Histone H3K9 me2/me3 marks are also upregated in various cancers and inhibition of H3K9me2 and H3K9me3 methylation by small molecule inhibitors of histone methyltransferases inhibit cancer progression [25, 26].

IV.ROLE OF HISTONE ACETYLATION IN NORMAL DEVELOPMENT, EPIGENETIC REPROGRAMMING AND CARCINOGENESIS

Various studies have shown that histone acetylations are upregulated during various stages of embryonic development[12]. Recent studies have shown that small molecule inhibition of histone deacetylases increase IPSC efficiency[27]. Also many studies have shown inhibition of histone deacetylases inhibit cancer growth of various cancer cells[28]. Various reports have shown that there is upregulation H3 and H4 acetylation marks during development of spinal cord and cerebral cortex [29, 30].

V. CONCLUSION

Epigenetic modifications are the important mechanisms involved in normal the development processes, regeneration and progression of various diseases like cancer. So any modification of epigenetic change help in prevention of diseases, as well as have an important role in increasing efficiency of stem cell generation as well as help in study of developmental processes in a better and efficient manner.

[1] Jin, B., Y. Li, and K.D. Robertson, *DNA methylation: superior or subordinate in the epigenetic hierarchy?* Genes & cancer. **2**(6): p. 607-617.

[2] Katsuyama, T. and R. Paro, *Epigenetic reprogramming during tissue regeneration.* FEBS letters. **585**(11): p. 1617-1624.

[3] Li, H., *Epigenetic and Signaling Pathway Regulation in Hair Cell Regeneration.* Cellular & Molecular Medicine: Open access.

[4] Loscalzo, J. and D.E. Handy, *Epigenetic modifications: basic mechanisms and role in cardiovascular disease (2013 Grover Conference series).* Pulmonary circulation. **4**(2): p. 169-174.

[5] Bannister, A.J. and T. Kouzarides, *Regulation of chromatin by histone modifications.* Cell research. **21**(3): p. 381-395.

[6] Zhou, Y., et al., *Epigenetic Modifications of Stem Cells.* Circulation research. **109**(9): p. 1067-1081.

[7] Vogel, T. and S. Lassmann, *Epigenetics: development, dynamics and disease*, Springer.

[8] Mirabella, A.C., B.M. Foster, and T. Bartke, *Chromatin deregulation in disease.* Chromosoma. **125**(1): p. 75-93.

[9] Xu, W., et al., *Epigenetics and cellular metabolism.* Genetics & epigenetics. **8**: p. 43.

[10] Lu, D., *Epigenetic modification enzymes: catalytic mechanisms and inhibitors.* Acta Pharmaceutica Sinica B. **3**(3): p. 141-149.

[11] Kim, J.K., M. Samaranayake, and S. Pradhan, *Epigenetic mechanisms in mammals.* Cellular and Molecular Life Sciences, 2009. **66**(4): p. 596.

[12] Saksouk, N., E. Simboeck, and J.r.m. DÃ©jardin, *Constitutive heterochromatin formation and transcription in mammals.* Epigenetics & chromatin. **8**(1): p. 3.

[13] Dong, X. and Z. Weng, *The correlation between histone modifications and gene expression.*

[14] Michalak, E.M. and J.E. Visvader, *Dysregulation of histone methyltransferases in breast cancerâ€“Opportunities for new targeted therapies?* Molecular oncology. **10**(10): p. 1497-1515.

[15] Ratnakumar, K., A. Kapoor, and E. Bernstein, *Regulation of chromatin structure and transcription via histone modifications*, in *Post-Translational Modifications in Health and Disease*, Springer. p. 365-385.

[16] Esteller, M., *Epigenetics in cancer.* n Engl j Med, 2008. **2008**(358): p. 1148-1159.

[17] Messerschmidt, D.M., B.B. Knowles, and D. Solter, *DNA methylation dynamics during epigenetic reprogramming in the germline and preimplantation embryos.* Genes & development. **28**(8): p. 812-828.

[18] Struhl, K., *Cancer: Is DNA methylation of tumour suppressor genes epigenetic?* Elife. **3**: p. e02475.

[19] Gopalakrishnan, S., et al., *DNMT3B interacts with constitutive centromere protein CENP-C to modulate DNA methylation and the histone code at centromeric regions.* Human molecular genetics, 2009. **18**(17): p. 3178-3193.

[20] De Carvalho, D.D., J.S. You, and P.A. Jones, *DNA methylation and cellular reprogramming.* Trends in cell biology. **20**(10): p. 609-617.

[21] Liu, J., et al., *Chromatin landscape defined by repressive histone methylation during oligodendrocyte differentiation.* Journal of Neuroscience. **35**(1): p. 352-365.

[22] Stewart, S., Z.-Y. Tsun, and J.C.I. Belmonte, *A histone demethylase is necessary for regeneration in zebrafish.* Proceedings of the National Academy of Sciences, 2009. **106**(47): p. 19889-19894.

[23] Chen, P., et al., *Effect of BIX-01294 on H3K9me2 levels and the imprinted gene Snrpn in mouse embryonic fibroblast cells.* Bioscience reports. **35**(5): p. e00257.

[24] Marion, R.M., et al., *Telomeres acquire embryonic stem cell characteristics in induced pluripotent stem cells.* Cell stem cell, 2009. **4**(2): p. 141-154.

[25] Tian, X., et al., *Histone lysine-specific methyltransferases and demethylases in carcinogenesis: new targets for cancer therapy and prevention.* Current cancer drug targets. **13**(5): p. 558-579.

[26] Li, J., et al., *Role of several histone lysine methyltransferases in tumor development.* Biomedical reports. **4**(3): p. 293-299.

[27] Huang, C. and J.C. Wu, *Epigenetic modulations of induced pluripotent stem cells: novel therapies and disease models.* Drug Discovery Today: Disease Models. **9**(4): p. e153-e160.

[28] Halsall, J.A. and B.M. Turner, *Histone deacetylase inhibitors for cancer therapy: An evolutionarily ancient resistance response may explain their limited success.* BioEssays. **38**(11): p. 1102-1110.

[29] Cho, B., et al., *Changes in the histone acetylation patterns during the development of the nervous system.* Experimental neurobiology. **20**(2): p. 81-84.

[30] Ceccacci, E. and S. Minucci, *Inhibition of histone deacetylases in cancer therapy: lessons from leukaemia.* British journal of cancer. **114**(6): p. 605-611.