Histone Methylation in Relation with Clinical Pathological Parameters in Prostate Cancer

Marine Daures1,2, Marjolaine Ngollo1,2, Mouhamed Idrissou1,2, Gaëlle Judes1,2, Khaldoun Rifaï1,2, Frédérique Penault-Llorca2,3, Yves Jean Bignon1,2, Laurent Guy1,4 and Dominique Bernard-Gallon1,2*

1Department of Oncogenetics, Centre Jean Perrin Clermont-Ferrand, France
2Department of Oncogenetics, University Clermont Auvergne, France
3Department of Biopathology, Centre Jean Perrin, France
4Department of Urology, CHU Gabriel Montpied, France

Short Communication

DNA and histone methylation are both modifications closely linked to stable repression. However, previous studies have shown that methylation repression by EZH2 could be an independent epigenetic mechanism of DNA methylation [1]. EZH2 protein and H3K27me3 marks appear to favor the development of prostate cancer by modulating gene expression. These data underline the importance of EZH2 and H3K27me3 in cancer development and opening an interesting strategy to modulate tumor progression. Several studies show that EZH2 has all of the oncogene properties because its over expression stimulates cell proliferation, invasion and promotes tumor growth in vivo conditions [2-5]. Conversely, EZH2 inhibition causes an arrest in cell cycle progression and abrogates tumor growth as well as metastases formation [6]. Increase of EZH2 expression observed in human prostatic tumors strongly suggests its involvement in carcinogenesis. Ngollo “et al.” [7] demonstrated the role of H3K27me3 histone mark on RARβ2, ERA, PGR, RGMA, SRC3 and EZH2 genes regulation [7]. This study separated two groups of genes in tumor tissues: genes with a high level of H3K27me3 (RARβ2, PGR, ERA and RGMA) with level of EZH2 correspond to an increase of gene expression. The small percentage of H3K27me3 mark on EZH2 and SRC3 may partly explain the increase in their expression in prostate cancer [8,9]. In addition, this study showed a correlation between variation in H3K27me3 mark and clinical pathological parameters: Gleason score, baseline PSA and clinical stage. Only Gleason score has allowed significant classification of patients in their respective groups and clinical stage correlates with the increase of H3K27me3 mark. Furthermore, these results suggest that PSA level increase is not necessarily associated with H3K27me3 epigenetic marks. For example, previous studies showed that APC promoter hypermethylation not correlated with PSA level suggesting that PSA level is not necessarily associated with epigenetic changes [10,11]. Therefore, the increase of H3K27me3 marks on RARβ2, PGR, ERA and RGMA is significant in the group of patients with a Gleason score ≥7 compared to the healthy group. This increase is all the more significant in the group with a score> 7 which represents the most advanced prostate cancer forms, synonym of poor prognosis. These data establish the role of H3K27me3 as an epigenetic marker involved in neoplasia. The increase of H3K27me3 repressive mark in prostate cancer is probably related to an over expression of the EZH2 protein. For example, when prostate cancer cell lines are treated with an EZH2 inhibitor, the expression of RARβ2, PGR, ERA and RGMA genes are increased. On the other hand, his tone demethylases are epigenetic actors that play a crucial role in prostate cancer by acting as tumor suppressor or as oncogene [12]. Depending on the histone tone mark, demethylases activate or repress transcription of genes. Demethylases jumonji domain containing 3 (JMJD3) and ubiquitously transcribed tetratricopeptide repeat, X chromosome (UTX) are both specific of H3K27me3 and thus play a role of transcription activator. JMJD3 and UTX are involved in developmental process by control of HOX gene [13]. However, their expressions are deregulated in cancer cells. Studies have highlightedJMJD3 role in development of various kinds of cancer [14-17] including prostate [18]. Daures “et al.” [19], showed simultaneous deregulation of JMJD3 and EZH2 in prostate cancer cell lines (PC-3 and LNCAP) compared to normal line (PWR-1E) and in human prostate biopsies and suggest a role of JMJD3 in the androgen receptor pathway. This study also identified three target genes of both proteins: ERA, RARβ2 and RGMA and established a privileged interplay between JMJD3 and RARβ2 in the most aggressive cell line PC-3.
In conclusion, H3K27me3 enrichment of RARβ2, PGR, ERα and RGMA and their regulation by JMJD3 and EZH2 in combination with clinical parameters such as the Gleason score, could serve as a prognostic biomarker of prostate cancer. Early studies have shown the role of histone modifications as prognostic markers. Indeed, a decrease in H3K4me2 and H3K18ac marks was observed in patients with prostate cancer compared to healthy patients [20-23]. Beyond the prognostic aspect, studies demonstrated that histone methylation plays a major role in stage of disease and estimate the risk of recurrence [24]. These preliminary results should make possible to identify relevant prognostic markers and, eventually, to have an epigenetic classification of prostate cancers, in view of the development of novel epipodugs.

References


