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Lysine methyltransferase methylation reaction and gene silencing in the screening of cancer development

Reação de metilação da lisina metiltransferase e silenciamento de genes no rastreamento do desenvolvimento do câncer

Reacción de Metilación de Lisina Metiltransferasa y Silenciamiento de Genes en la Detección del Desarrollo del Cáncer

RESUMO

Objetivo: Investigar os diferentes papéis da metilação da proteína lisina metiltransferase H3K9 no silenciamento de genes, associados ao rastreamento do desenvolvimento do câncer. Métodos: Trata-se de uma revisão de literatura, a partir da apresentação e da síntese dos estudos selecionados acerca do papel da metilação da proteína lisina metiltransferase H3K9 e silenciamento de genes. As bases de dados utilizadas na triagem de material, foram as plataformas de busca: Nature, Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (SciELO) e Science Direct. Resultados: Foram identificados 32 estudos relacionados ao tema proposto. Após triagem dos registros obtidos pela busca nos bancos de dados, obteve-se como produto final dos artigos incluídos na revisão, 6 trabalhos que retratavam a proposta do estudo. Conclusão: Apresentou-se uma visão geral atualizada e específica dos efeitos celulares e moleculares subjacentes à atividade de H3K9 no desenvolvimento e progressão do câncer.

DESCRIPTORIOS: Câncer; Metilação; Lisina; Metiltransferase.

ABSTRACT

Objective: To investigate the different roles of lysine methyltransferase H3K9 methylation in gene silencing associated with screening for cancer development. Methods: This is a literature review, based on the presentation and synthesis of selected studies on the role of lysine methyltransferase H3K9 protein methylation and gene silencing. The databases used in the material screening were the search platforms: Nature, Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (SciELO) and Science Direct. Results: 32 studies related to the proposed theme were identified. After screening the records obtained by searching the databases, 6 works that portrayed the study proposal were obtained as the final product of the articles included in the review. Conclusion: An updated and specific overview of the cellular and molecular effects underlying the activity of H3K9 on cancer development and progression is presented.

DESCRIPTORS: Cancer; Methylation; Lysine; Methyltransferase

RESUMEN

Objetivo: Investigar los diferentes roles de la metilación de la lisina metiltransferasa H3K9 en el silenciamiento génico asociado con el cribado del desarrollo del cáncer. Métodos: Se trata de una revisión de la literatura, basada en la presentación y síntesis de estudios seleccionados sobre el papel de la metilación de la proteína lisina metiltransferasa H3K9 y el silenciamiento génico. Las bases de datos utilizadas en la selección del material fueron las plataformas de búsqueda: Nature, Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (SciELO) y Science Direct. Resultados: se identificaron 32 estudios relacionados con el tema propuesto. Tras el cribado de los registros obtenidos mediante la búsqueda en las bases de datos, se obtuvieron 6 trabajos que retrataban la propuesta de estudio como producto final de los artículos incluidos en la revisión. Conclusión: Se presenta una descripción general actualizada y específica de los efectos celulares y moleculares que subyacen a la actividad de H3K9 en el desarrollo y la progresión del cáncer.

DESCRIPTORIOS: Cáncer; Methylation; Lisina; Metiltransferasa

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INTRODUCTION

Cancer stands out for being one of the main objects of study today, due to its epidemiological relevance, mainly caused by the global social and economic impacts resulting from the increase in its incidence, since this is established as the second leading cause of death in the world, according to data presented by the World Health Organization.¹

From this perspective, several studies have been carried out with an emphasis on understanding the emergence of this disease, aiming to track different signaling pathways that can trigger the onset of cancer. Based on those that are under constant evolution regarding the conception of these factors, DNA methylation and histone alteration stand out, responsible for playing a role in gene expression, with changes reported in several types of cancer.^{2,3}

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Starting from a first analysis, it appears that histones - a specific type of proteins present in lysosomes - are susceptible to various types of covalent modifications, these being; methylation; and acetylation; ubiquitylation; sumoylation and phosphorylation. DNA methylation is the best characterized epigenetic modification in the literature and recognized as a gene silencing mechanism.⁷

This process basically consists of the addition of a methyl radical (CH₃) on carbon 5 of Cytosine, usually followed by Guanine (dinucleotide CpG), catalyzed by DNA methyltransferases (DNMTs) enzymes. Among the several families of expressed proteins, there is the Lysine Methyltransferase (PKMT), which acts mainly in the methylation of lysine residues in histones, being able to catalyze the transfer of up to three methyl groups to lysine residues.^{7,8} Thus, in PKMT, there is the Histone-lysine N-methyltransferase 2 (G9a), responsible for the methylation of Lysine 9 in histone H3, associated with the methyltransferase H3K9, indicating acetylation of the 9 residue lysine in histone 3, being the genes, activated if such tag is acetylated and silenced if there is its methylation. This protein is directly responsible for the silencing of genes involved in the embryonic stage, being reported in several types of cancer, through the maintenance of the serine-glycine biosynthesis pathway.²⁹

On the link between H3K9 and DNA methylation, in *Neurospora*, DNA methyltransferase (DIM-2) forms a complex with Heterochromatin 1 Protein (HP1) and then DIM-5 Histone Lysine Methyltransferase (HKMT) methyl H3K9 so as to form H3K9me₃.^{10,11} After this event, the DIM-2-HP1 complex is recruited to a locus of nucleosomes positive for H3K9me₃, through the binding of HP1 to H3K9me₃, inducing DNA methylation. In *Arabidopsis*, however, DNA and H3K9 methylation are independent of their function and relationship. Thus, it is possible to verify that the Set or Ring domain of the HKMT KRYPTONITE (KYP) binds to methylated DNA and, as a consequence, the KYP searches for the nucleosomes, in order to

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methylate H3K9, in order to form H3K9me₂. Thus, H3K9me₂ recovers DNA methyltransferase Chromomethylase 3, in order to induce DNA methylation.^{12,13}

In mammalian cells, DNA methylation in large satellite repeats is reduced in histone lysine methyltransferases - SUV39h1 and SUV39h2 - with double knockout in embryonic stem cells (ES).^{14,15} Thus, SUV39h1-mediated H3K9 methylation and HP1 recruitment play a fundamental role in the recruitment of pericentromeric heterochromatin of HP1 α and HP1 β , interacting with DNA methyltransferase 3b.^{14,15}

However, from another perspective, other punctual changes in mammalian cells are also described. In ES, DNA methylation dependent on G9a - GLP and independent of histone methyltransferase activity *in vivo* has been described, ie, the catalytically inactive G9a partially restores the aberrant DNA methylation pattern in G9a cells. In HeLa, DNMT1 interacts with G9a, regulating G9a chromatin loading, and DNMT1 knockdown, inducing a reduction in H3K9me₂ levels.^{16,17}

In this perspective, although the chemical properties of PKMT protein methylation make it challenging from a technical point of view, obtaining a screening of biological mechanisms associated with influence on cancer development allows us to suggest that methylation may not occasionally be susceptible to other types of post-translational modifications. Furthermore, it is commonly accepted that a protein does not exist in a rigid, permanent and stable conformation, but in an unspecific set of diverse conformational parameters present in a variable and shifting equilibrium.^{17, 18} Thus, the present study aims to carry out a review that addresses the different roles of the methylation of the protein lysine methyltransferase H3K9 and gene silencing, in order to suggest and relate confluent parameters associated with the screening of the development of different types of cancer.

METHODS

This study has an observational, cross-sectional and qualitative approach. This is an integrative review, based on the presentation and synthesis of selected studies on the role of lysine methyltransferase H3K9 methylation and gene silencing, in order to relate to the screening of development and prognosis of various types of cancer described. To obtain, register and analyze the products obtained in the research, the following steps were taken: (1) Identification of the theme and formulation of the research question; (2) Elaboration of inclusion and exclusion criteria for articles; (3) Construction of instruments to collect relevant data from the articles found; (4) Evaluation and analysis of selected articles in the research; (5) interpretation and discussion of the results obtained; (6) Presentation of the review along with the theoretical framework on the subject.

The survey of studies obtained in the literature, in order to record the results, was carried out from January to April 2021. The databases used in the material screening were the search platforms: Nature, Medical Literature Analysis and Retrieval System Online (Medline), Scientific Electronic Library Online (SciELO) and Science Direct. The study gave priority to works published in English and Portuguese. The keywords searched were: Cancer, H3K9, Lysine and Methyltransferase. To carry out the tabulation of the articles, the following inclusion criteria were determined: articles published between 2011-2020, favoring

recent studies on the subject; texts available in full; scientific research classified as original and indexed in databases and articles available in Portuguese and English. Also excluded were: articles published prior to 2011; publications repeated in two or more databases; publications available in abstract form only; studies in letter format; works that did not have as study subjects the approach of the proposed theme.

At the end, the usefulness data in the articles were extracted based on information established according to the following variables: (i) the author and year of publication of the article; (ii) molecular studies, case reports and epidemiology; (iii) interaction mechanisms and protein expression analysis; (iv) relevance, originality and impact of the study on public health; (v) objective, contribution and conclusion of the study. Thus, under qualitative analysis, the studies were selected from the analysis of titles. Articles were designated for independent review of the abstracts. The abstracts of the selected articles were read in full and provided significant results, shown in tables later on.

RESULTS

After a systematic search, a total of 32 studies related to the role of methylation of the protein lysine methyltransferase H3K9 and gene silencing, associated with the screening of the development of different types of cancer, were identified, and these were

registered in quantitative correspondence after delimitation of the exclusion criteria, configured according to the established variables, with SciELO (n = 13), ScienceDirect (n = 7), Medline (n = 9) and Nature (n = 3), from the search based on the restriction of filters established by the access platforms, interleaving crossing of descriptors and addition of operators, obeying the inclusion and exclusion criteria, in order to restrict the search parameters and make the selection process of the studies found susceptible. After screening the records obtained by searching the databases, the final product of the articles included in the review was obtained from 6 works that portrayed the proposal of the theme, with the rest being discarded based on the following criteria; Inadequate search period (n = 6); Theme Divergence (n = 11); Search access intercurrency (n = 9); Relevance of the results obtained (n = 6). The product of the articles obtained for inclusion in the study is shown below (Table 1) and the schematic summary of the main findings (Figure 1).

DISCUSSION

The understanding of molecular epigenetic mechanisms has been developing over the years, substantially improving the understanding of the mechanisms of occurrence of post-translational histone modification (PTMs) and transcription regulation under normal and pathological conditions, with emphasis on the scree-

Table 1: Registration and Synthesis of Data selected in the research

Author Year	Title	Objective	Conclusion	Contribution
Sakamoto 2014	Role of protein methyltransferases in the development and prognosis of childhood acute lymphoid leukemias	To verify the role of gene expression encoding protein methyltransferases in the development and prognosis of childhood acute lymphoid leukemia	It was proven, in a leukemia cell line, that silencing the SMYD2 gene is able to reduce the rate of cell proliferation, which may be caused by alterations in the methyltransferase-H3K9 activity of this gene, both at the level of histone and not-histone proteins.	This is a pilot study in which it is possible to identify high levels of expression of genes encoding lysine methyltransferases in childhood Acute Lymphoid Leukemia samples, when compared to non-neoplastic marrow

Noh et al., 2014	p53 down-regulates SETDB1 gene expression during paclitaxel-induced cell death	To assess whether Paclitaxel affects SETDB1 HMTase expression during cell death and whether Paclitaxel induces cell death through G2/M regulation in human lung cancer cells	The studies concluded that PTX treatment, in fact, induces p53 and down-regulates SETDB1 in the transcript. SETDB1 promoter activity is increased to approximately 30-fold under normal conditions, but activity is significantly inhibited in the PTX-treated group. Furthermore, p53 transfection inhibits the activity of the SETDB1 promoter	The studies showed that the SETDB1 gene has expression dictated by the p53-dependent repressor complex reported in its promoter region. This study is relevant because it is the first work to indicate that the expression of the SETDB1 gene is regulated by a p53 tumor suppressor.
Tao, et al., 2014	Histone methyltransferase G9a and H3K9 dimethylation inhibits self-renewal of glioma cancer stem cells	Describe the role of Histone 3 in the methylation of lysine 9 (H3K9me2) and its G9a methyltransferases in cancer stem cells	The results indicate methylation of the histone transferase G9a and H3K9 act as the main change to regulate the self-renewal of the stem cell glioma, through direct repression in the CD133 and Sox2 promoters.	A set of hypotheses about the variety of evidences that pointed out that the repression of G9a is H3K9me2-dependent was verified and was one of the main aspects considered to establish the self-renewal of glioma cancer stem cells
Tachibana, et al., 2011	SET domain-containing protein, G9a, is a new favorite for lysine Mammalian Histone Methyltransferase with Hyperactivity and Specific Selectivity for lysines 9 and 27 of histone H3	Evaluate the responsible mechanisms during the regulation of the nuclear processes of histone H3 as transcription control and mitotic condensation	The data indicate that G9a has an enzyme of nature distinct from Suv39 h1 and its homologue h2, and that G9a, labeled with a fluorescent protein, was located in the repressive chromatin domain at centromeric loci, in the same region as the proteins of the Suv39 h1 family. This may indicate that G9a may contribute to the organization of the high order chromatin structure of non-centromeric loci.	The study presents a new understanding that G9a is a lysine H3 HMTase preference, showing stronger HMTase activity than Suv39 h1. The mutagenesis experiments demonstrated that the elevated enzymatic activity of G9a is also dependent on the first central residue in the SET domain, with arginine 899 in mice, showing a shift from histidine 320 to arginine at this same position in Suv39 h1.

<p>Tapias, et al., 2019</p>	<p>Major and Pro-oncogenic Lysine Methyltransferase SETDB1 Expression in Lung Cancer</p>	<p>To investigate the clinical significance of SETDB1 expression in the two main forms of non-small cell lung carcinoma (NSCLC), namely adenocarcinoma and squamous cell carcinoma, from a meta-analysis of diverse transcriptomic data sets and a systematic review of literature</p>	<p>The study revealed elevated levels of mRNA, SETDB1 in the NSCLC compared to non-cancerous control tissues. The data suggest the possibility of using SETDB1 mRNA Level as a marker for early detection of NSCLC</p>	<p>The results suggest a solid foundation for future research to evaluate SETDB1 as a diagnostic biomarker and/or its potential use as a therapeutic target in non-small cell lung cancer</p>
<p>Rowbothan, et al., (2018)</p>	<p>H3K9 methyltransferases and demethylases control lung tumor cell spread and lung cancer progression</p>	<p>To assess whether histone methyltransferase G9a, reported as a therapeutic target in many cancers, is characterized as a suppressor of aggressive lung tumor propagation cells (TPCs)</p>	<p>The study highlights the importance of choosing the best model of cell heterogeneity. It was possible to conclude, based mainly on cell lines and whole tumors, that G9a is oncogenic and a good target for epigenetic therapy</p>	<p>The authors present a new understanding of the cellular context and how specific tumor populations are critical in analyzing targeted epigenetic regulators in cancer for future progression screening and development of therapeutic strategies.</p>

Source: Prepared by the author

ning of different types of cancer. In this perspective, despite the prevalence of incipient evidence on the interaction of lysine methyltransferases among themselves and among other proteins, it is likely that there is a transcriptional control at the level of activity of the promoter of a gene encoding a methyltransferase regulated by another protein methyltransferase, which can conceive the existence of a common or coordinated regulator, which is active in the chain of several protein methyltransferases, which may indicate the presence of cancer. 2

Under an initial approach, dealing with this perspective, the study by Sakamoto LHT, et al. (2014) 19 verified that, after clinical and laboratory observation of genes expressed in patients, these expressed products, which have an association in transcriptional regulation, are supposedly related to some role in leukemogenesis or in the prognosis of patients. An intriguing finding in their study revealed a high correlation rate from the expression levels of genes that were shown to be distinctly ex-

pressed in leukemias.

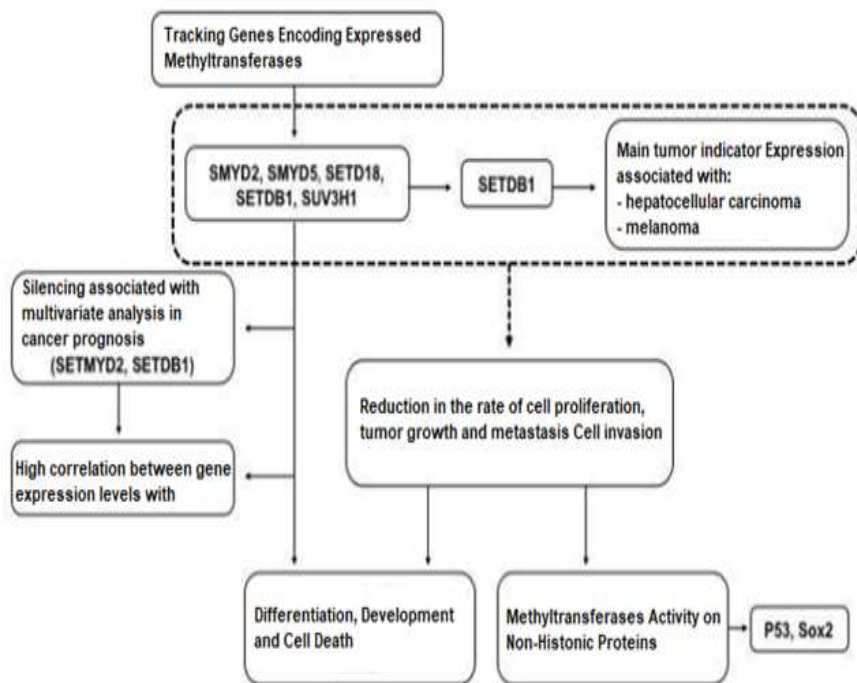
Relating to Noh HJ, et al. (2014), 20 performed with pulmonary lineage cells, a re-expression of p53 protein was evidenced, with subsequent decrease of SETDB1 - lysine methyltransferase - with H3K9me activity under treatment with chemotherapy (paclitaxel), which corroborates during the process of chromatin compaction during differentiation, development and cell death. Furthermore, the same study described that p53 participates by binding to the SETDB1 promoter and inducing H3K9me3, being designated the subsequent methyltransferase-related expression SUV39H1. Therefore, the p53 complex, induced by chemotherapy, increases H3K9me3 in the SETDB1 region, and this increase may be able to decrease the action of the promoter, causing a low expression of this gene.

As previously described, SETDB1 plays an important role in the detection of tumors, through the significant expression associated with hepatocellular carcinoma and melanoma. On the other hand, SET-

DB1 silencing appears to inhibit cell proliferation, cell invasion, tumor growth and metastasis in several types of cancer. SETDB1 can impact the cancer phenotype, acting on different substrates, having as its main target H3K9 and in addition, other highly relevant suppressors are also described, including the tumor suppressor TP53 and AKT kinase, being an important determinant in several molecular events, not just in terms of chromatin. Tapias PC, et al. (2019), 21 was able to identify in their study overexpression of SETDB1 related to the clinical features of lung cancer patients with two types of non-small cell lung cancer, namely adenocarcinoma and spinous cell carcinoma.

In a study by Tao H, et al. (2014), 22 the majority of CD133 positive cells were found to be H3K9me2 negative, both in glioma tissues and in cell culture, although most cancer cells were detected to be H3K9me2 immunopositive. The authors associated these results with G9a-H3K9 dependent on one of the fundamental

Figure 1: Schematic summary of the main findings



Source: Amorim MT, et al., 2021

barriers of cancer stem cell self-renewal. In order to test these hypotheses, the loss and gain of function of G9a was observed and with this, they discovered a selective inhibitor (bix 01294), responsible for stimulating Sox2 and CD133 and corroborating the increased rate of formation of cancerous glioma spheres in stem cells.

According to Tachibana M, et al (2007), 23 in a study carried out with germ cells, the authors describe a restricted relationship of the expression of the G9a protein to spermatogonia and initiating leptotene spermatocytes. In order to assess the role of G9a in cell development, the expression of G9a in testes was analyzed and a profile of G9a expression was found; GLP similar to that of PLFZ antibodies, suggesting that the expression of these proteins is not constant

but constantly regulated during spermatogenesis. A dynamics of H3K9 methylation was verified during male meiotic prophase, from which H3K9me2.1, mediated by G9a, was lost in pachytene spermatocytes. These data suggest that H3K9 methylation during meiotic prophase is dynamically regulated from the combination of proteins and expressed genes. Therefore, the insights provided allow us to suggest how the effects of H3K9 methylation and demethylation reactions may regulate primordial functions that may affect cell development and differentiation.

These epigenetic regulators can be considered very attractive targets against cancer and, in view of this, the emphasis by studies that assess the effectiveness of screening strategies for the progression of

these factors, has become increasingly necessary in consideration of the behavior of tumor cells. Rowbotham SP, et al. (2018), 24 found that inhibition of G9a, leads to increased tumor propagation cell function and boosts metastatic tumor propagation, also identified G9a by repressing a gene signature associated with regulators in mutant KRAS and ECM, cite Mmp10, which participates in tumorigenicity of tumor cells depleted in G9a. Furthermore, inhibition of H3K9 KDMs, also described by the authors, may be a beneficial alternative treatment for advanced lung adenocarcinoma. Thus, when evaluating the epigenetic dependencies of tumor propagating cells, the study could reveal an alternative potential for therapeutic intervention in advanced lung cancer.

CONCLUSION

In agreement with the results presented, it can be seen that after the advent of techniques for genomic analysis, the capacity for comprehensive screening of studies on the epigenome of human cancers, developed and opened new precedents for the provision of accurate information on prevention strategies, diagnosis and prognosis associated with the development of this pathology. Here, we provide an up-to-date and specific overview of the cellular and molecular effects underlying the activity of H3K9 on cancer development and progression, presenting the various targeting strategies currently in different types and stages of cancer, with promising effects associated with its progression, corroborating as an autonomous agent that, together with technological advances, may help to understand the "epigenomic landscape" and its relationship with gene expression profiles.

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