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A Survey on Functions of Polycomb Group Proteins

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ABSTRACT

The biological individual embryonic development and cellular proliferation, differentiation are strictly regulated by multiple genes. PcG gene group is a kind of important development related genes, PcG proteins can be in the form of protein complexes involved in inhibition of HOX genes expression, in order to maintain the body's normal development and cell proliferation and directional differentiation, for instance, PcG protein formation of chromatin complex of embryo and stem cell self-renewal played an important role. If the hox gene transcription regulation of protein function can be caused by changing the hox gene expression patterns and abnormal cell proliferation, differentiation, and presents some special pathological phenotypes, such as abnormal hematopoiesis, prostate cancer, breast cancer, abnormality of individual development, and histone modification plays a key on PcG silence.

Key words: PcG protein; HOX genes; Gene expression

INTRODUCTION

0 Hox genes (Hox gene) is a kind of important development related genes, but pattern "space-time" decides to directional differentiation and proliferation of cells through its specific expression, and regulate the development of the body tissues and organs. Once the HOX genes or dysfunction of the transcriptional regulate proteins, it will directly affect the cell proliferation and differentiation process. In fruit flies and vertebrates, homeotic/Hox genes are in the front axle expression in embryonic development in the specific areas, and homeotic/Hox genes expression, in the form of the "time", coordinate the finished mutual antagonism by the PcG (polycomb group)/TrxG (Trithoraxgroup) protein functions. In vertebrates, fruit flies, and even plants, the PcG/TrxG proteins are composed of a set of very conservative in evolutionary cellular memory system, so the homeotic/Hox genes in the body remain stable in the process of development, and pass down generation after generation in the cell. Thus, when the PcG mutations in the gene will cause abnormal expression of homeotic/Hox genes, and eventually lead to the body dysplasia and deformities. In mammals, PcG gene mutations can also lead to promote cancer gene expression in cells increases, even tumorigenesis [1]. In this paper, the general research of PcG protein and its function were reviewed.

1. The PcG group overview and PREs discovery

PcG genes was originally found in fruit flies, their synergy sustained the inhibition of the HOX genes, and fruit flies at present was the best model for animal research PcG/TrXG system [2]. Drosophila embryo research showed that "space-time" of HOX genes expression patterns were originally affiliated to the gap. The two kinds of protein with DNA bind activities mostly, and its distribution with a certain regional. The gap class of protein was the direct inhibition of HOX genes, controlled range overlap of two classes of protein and the role of mutual antagonism,

jointly established the specific HOX gene expression patterns in the cell. The drosophila embryo generated after about 4h, the above two kinds of protein gene expression shut down. For establishing HOX gene expression patterns, the PcG and TrXG protein maintained among them, the PcG (polycomb group) protein mainly suppressed cell gap protein by closed HOX genes expression, while TrxG (trithorax group) protein ensured HOX genes expression to continue activating [3].

A feature of is PcG protein was performed by many protein complexes, these complexes with chromatin formed distinctive and discontinuous nucleoprotein structure called the PcG [1]. Biological research showed that three unique PcG protein complexes had been purified, mainly including PRC1 (Polycomb repressive complex1), PRC2/3, PhoRC (Pleiohomeotic repressive complex). PRC1 included Ring1B Ring1A, BMI - 1, PC3 (Polycomb3), PRC2/3 and EZH2 (human homolog of enhancer of Zeste2), EED (Embryonic ectoderm development), Nurf55; PhoRC included Pho and DSFMBT. Three PRC2 / specific methylation of histone H3 lysine27, and EZH2 was catalytic subunit, other components also played an important role; PRC1 had inhibition of the nuclear small weight and transcriptional activity, could make the H2A Lysine119 ubiquitin; Pho PhoRC of subunits with DNA binding activity, Dsfmbt had combined with modified histones activity, the author analyzed by fluorescence polarization, when H3 and H4 sheets formed four or three methylation, Dsfmbt protein MBT repeated selective combination to the N end of H3 and H4 [2]. But it had found that most of the PcG was not DNA, the report gene detection and CHIP technology revealed specific role in cis element (cis - regulatory sequences). So these results showed that Polycomb responsed elments (PREs). Then it was also found that the sequence of specific proteins was related Pho PcG protein transcription factors (mammals YY1 homologue). The ChIP experiments showed that the transcriptional activation of genes did not have PcG protein combination of PREs. But the latest research showed that the PcG protein component combined the PREs, but in the proximal PREs, the combination of the PcG protein decreased significantly [4].

2. PcG protein function

Cell proliferation differentiation process influenced by HOX genes expression patterns, while the class of PcG protein and TrX protein regulated every developmental stage of the HOX gene expression of cells. If the HOX gene transcription regulation of protein function changed by the HOX genes expression patterns and abnormal cell proliferation differentiation, some special pathological phenotypes.

PcG protein formation of chromatin complex of embryo and stem cell self-renewal played an indispensable role, and was often being degraded in cancer cells. According to reports in the literature, in the human fibroblast cells, Genome- wide used positioning analysis technical tested PcG protein complexes of target genes, it was found that the genes for embryonic development and cell fate determination played a very important role. And it was found that if the missing PRC2 components EZH2, EED, SuZ12 and PRC1 BMI - 1 40 genes in human embryonic fibroblasts suppressed. PcG gene not only regulated the necessary embryonic development and kept the number of adult stem cells, such as: the regeneration of neural stem cells on hematopoietic and BMI - 1t and hematopoietic stem cell failures. With PcG genes in regenerative cells differentiation and development played the important role to maintain consistent some PcG genes. The entities and hematopoietic cancers was expressed, and further found that PcG targeted in some tumor suppressor genes, and these genes declined in expressing in tumor [5].

Mammals PcG homologous proteins was related to human hematopoiesis abnormal. The gene cloning and positioning in chromosome 10 p13 had total of 959 591 591 adenine, cytosine, guanine and thymine 975. The gene mutation could work with c - myc oncogene, caused a B cell non-hodgkin's lymphoma. Because the bmi - 1 gene encoding protein had the function of promoting transgenic mice occuring lymphoma and was considered relating to the occurrence of acute leukemia in mice. Due to the bmi of phenotype - 1 transgenic mice and fruit flies mutation phenotype were very similar, its function was also conservative evolution. The results showed that bmi-1 was the function of proteins in hematopoietic cells specificity of spectrum and differentiation stage, did not seem to be necessary during embryogenesis, but for some adults the proliferation of hematopoietic cell lineage was very important. Bmi-1 gene expression patterns, unlike most other PcG genes, was in primitive hematopoietic cells expressing high levels, and in only a few conceal CD342 mature cells. ZNF144 MEL18 genes was a human PcG homologous genes, and genes were highly homologous with bmi-1. The gene was in high expression in placenta, lungs and kidneys, but in the liver, pancreas and skeletal muscle in the expression level was low. The gene was located on chromosome 12 12 q22 belt. Because MEL18 transgenic mice genetically engineered mice with bmi having early T, B lymphocyte differentiation barrier. Due to its phenotype and excessive expression of HOXA10 or HOXA3 mice bone marrow hematopoietic cells, both might be affected by the same HOX genes expression and

caused abnormal cell differentiation. Under normal circumstances, MEL18 genes encoded proteins with tumor suppressor activity. But unlike drosophila PcG protein, MEL18 gene encoding protein could bind to DNA directly, it had become the first identified combined with DNA direct characteristics of PcG proteins. Due to different MEL18 genes in the origin of all kinds of tumor cells, the cells were expressed, and there were already signs for HOX, c - myc and the BCL-2 the regulation of gene transcription being affected by MEL18 protein, according to Kanno study, such as MEL18 proteins controlled at least two different biochemical events: (1) the transcriptional regulation of HOX genes; (2) cell growth/death control.

PcG proteins in the X chromosome inactivated and also played an important role in tumor formation. EZH2 could specificity of methylation nucleosome histone H3 lysine (H3 - K27) from 27. H3-K27 methylation promoted the PRC1 complex components (PC) combined into one element in the N of histone H3 tail ", indicating that PcG mediated gene silencing contacted between histone and methylation. EZH2 mediated H3-K27 methylation promoted the combination of PC to raise PRC1 complex signal. EED - EZH2 PcG protein complexes and methylation of histone H3 27th lysine (H3-K27) contributed to gene silencing, H3-K27 methylation in imprinting (imprinting) X chromosome inactivated [2]. Cells and embryonic cells were in embryo in vitro during X chromosome inactivated, EED-EZH2 PcG protein complexes inactivated X chromosome (Xi), and also with H3-K27 methylation. This kind of compounds in Xi raised and methylation depended on XistRNA, rather than its silence function itself. EZH2PcG protein mediated H3-K27 methylation were shown in mark and random X chromosome also inactivated.

It was reported [6] that EZH2 played an important role in the evolution process of human prostate cancer. EZH2 gene located on chromosome 7 q35 position, the gene in the genome structure covered nearly 40 KB, contained20 exon, opened reading coding box distribution on 19 exons. EZH2 gene and flies E(z) gene sequenced alignment, in n-terminal section had three highly conservative sequence, in the C terminal had a highly conservative SET (Su (var) 3-9, E (z) and t rit horax) area. In vertebrate PcG homologue contained two evolutionary conserved region. N chromatin area (chromodomain) was essential for PcG protein combined with chromatin. The mutation of PcG protein lost chromatin binding ability. And conservative C end of PcG protein function was very important. C genes for missing mutant lost inhibitory activity. E (Z) and its homologue all vertebrates contained highly conservative SET area. EZH2 protein also contained highly conservative SET area. SET in gene expression related to chromosome regulator. EZH2 mediated transcription inhibition relied on complete SET area. EZH2 could inhibit the chromatin structure of target genes, promoted cell proliferation and stimulated the proliferation of tumor cells. That was meant it could be a new tumor markers, and gradually showed its potential clinical value. Their DNA chips used in the study of prostate cancer, the results showed that in comparison with localized prostate cancer, 55 of metastasis of prostate cancer gene expression raised obviously, 480 gene expression significantly lowered. Column in the metastasis of prostate cancer first raised gene EZH2, targeted on EZH2 siRNA double-stranded cut EZH2 to the amount of protein in prostate cancer in vitro and inhibit cell proliferation. Compared with localized prostate cancer and benign lesions, metastasis of prostate cancer EZH2 transcription increased significantly. From primary prostate cancer metastasis, EZH2 genes were activated. At the same time, there were multiple gene transcription being suppressed, rather than being activated. This inhibition had the characteristics of group inhibition. These repressed genes, many of tumor suppressor genes were inhibiting tumor evolution process. In addition, it was also found that EZH2 was mediated prostatic cell proliferation and the role of transcription. Anyway, because the abnormal expression of EZH2 gene transcription disordered mechanism of memory, might participate in the process of fatal prostate cancer, there might be genetic groups in metastatic disease inhibition mechanism. In addition there also reported a cell from the udder of normal resting EZH2 expression, invasive breast cancer compared with normal breast epithelium EZH2 protein was raised. EZH2 protein matrix analysis of breast cancer, and the result was similar with prostate cancer, which were relative with benign breast tumor, limitations of breast cancer, metastasis of breast cancer with high EZH2 protein expression.

EZH2 mechanism might be EZH2 in lm-prb - E2F pathway downstream, because the phosphorylated lm-prb (Retinnoblastoma protein) combined E2F, E2F start S phase inhibition gene transcription, dock lm-prb - E2F complex combination in DNA promoter site, in situ inhibiting the transcription of the promoter, the EZH2 could stimulate the proliferation and inhibition of target genes [7]. Activation of p53 by inhibiting EZH2 promoter inhibition of the expression of the gene, also through the lm-prb - E2F pathway mediated G2 / M block, by using the expression of EZH2 in p53 inhibits, tumor would also become a new way of controlling the evolution of cancer cells [8].

3. The recruitment of PcG protein and PcG protein complex regulatory mechanism of target genes

How to be recruited to the PREs PcG has different models: a view was that EzH2 and Eed could be directly with Pho in vitro, so Pho directly recruited PRC2 to PREs, and PRC2 could make teimethylates histone H3K27 PREs, and thus provided PRC1 PC protein binding sites. But some of the latest research challenged the model, the CHIP of quantitative analysis showed that in the PREs nucleosome is missing. Others reported Pho and Ph PRC1 subunits and Pc directly interacted, and they could combine to bare DNA in vitro [4].

But after the PcG protein complexed with PREs specific, how to accomplish the target gene regulation was not clear. It could be through by following mechanisms: a. in the form of more protein complexed with PREs combination of Hox genes transcription regulation zone, controlled the DNA of chromatin packaging into "heterochromatin" structure, thereby specific transcription could be into DNA control area; B. the stability of the nucleosome was arranged to prevent complex (such as SWI2SNF) of nucleosome remodeling; C. TAF **O** proteins were activated to restrain activity of transcription mediating transcription; D. The change of histone acetylation; E. the interference between the promoter and enhancer of interaction; F. The complex of formation silent child-promoter. These effects were usually mediated by PcG protein combined with the PRE, but other studies found that PcG proteins also combined with some outside the PRE core promoter, these sites had important function, in some cases, might assist in the upstream of the PRE work [9].

4. Epigenetics and PcG silence

Epigenetic events included DNA methylation and histone modification after translation, such as acetylation modification, etc. The change of chromatin structure controlled the transcription of a variety of cell models and histone modification had been recognized as a kind of coding mechanism, called histones password, the password could be some protein complex identification, the protein complexes could specific recognize and combine to the modification of histone, causing a series of biological effects, Polycomb inhibition and Trithorax promoters played a main role in the event of epigenetics protein complexes [5].

It was reported that the gene closed, H2K27, H3K9, H4K20me3 existing in the upstream controlling area, promoters and coding regions. And in the case of gene activation, the three methylation in the promoter and the coding regions disappeared, illustrating these histone modification played a key role for PcG silence [4].

5. Outlook

Embryonic development and its regulation mechanism of an organism had long been a hot spot, but because of its extremely complex gene regulatory network, the research is tough. PcG gene families in both the fruit fly and the orientation of development in mammals, cell proliferation, differentiation, apoptosis and other phenomenon has played a decisive role in life. More important significance is that in the form of more protein complexes of the PcG protein family regulate the expression of target genes, at this point, it enables people to update understand of gene expression regulation.

With the deepening of the PcG protein and protein complexes TrxG research, people further understand cellular memory mechanism. In exploring the development and tumor formation on the basis of common ground between the gene expression of the research development of space and time order and programmed process, malignant tumors of the same gene expression in the evolution process of disorder of time and space and randomness were found. For the level of structural genomics and functional genomics research evolution mechanism of malignancy, the useful diagnostic and prognostic evaluation marks are found and new way of discovering new therapeutic targets open up. Such as clinically prostate cancer, breast cancer mortality remains high, metastatic prostate cancer, breast cancer EZH2 protein expression is significantly higher; If the high expression of EZH2 localized prostate cancer, breast cancer, the clinical prognosis is poorer, therefore EZH2 can be used as tumor markers in monitoring the evolution of prostate cancer, breast cancer.

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