Interactions Between REST/Co-REST and LSD1/HDAC1/SIN3A/FOXK2 Complexes in Tumors.

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Abstract. RE1-silencing transcription factor (REST) is an encoded protein member of the Kruppel-type zinc finger transcription factor family. Depending on the tissue, variations in REST concentrations can result in different diseases. Proteins as LSD1, HDAC1, SIN3A and FOXK2 form different complexes with REST and CoREST and they can even interact with each other. In Prostate cancer, LSD1 inhibition can markedly decrease Protein Kinase B phosphorylation, known as AKT. Histone Deacetylase protein (HDAC1) have the function of catalyze the acetylation of lysine residues on the N- terminal of the core histones. The experiments suggest that Retinoblastoma protein (Rb) can recruit HDAC1 and cooperate to suppress the E2F-regulated promoter of the gene. In addition to the regulatory function of SIN3A in cortical neuron differentiation, it's been identified that by forming a complex with HADC1 it can act as a suppressor of STAT3 transcriptional activity. In hepatocellular carcinoma FOXK2 knockdown can inhibit the proliferation, colony formation, migration an invasion of HCC cells. The machinery and the pathway will be determined by the type of tumor, the tissue that it is located and the type of target cell. The importance of studying these complexes seems to be the best way to better understand cancer physiopathology and to help develop new drugs that can reach these tumors without affecting functional cells.

Keywords. REST, CoREST, LSD1, HDAC1, SIN3A, FOXK2, Cancer.

1. Introduction

RE1-silencing transcription factor (REST) is an encoded protein member of the Kruppel-type zinc finger transcription factor family. REST has two repression domains known as RD1 (N-terminal), RD2 (C-terminal) with ninth C-terminal zinc finger, lysine-rich and proline-rich domains, a DNA binding domain of eight zinc fingers, two nuclear localization signals, and a phosphodegron (E1009/S1013 or S1027/S1030). REST can recruit a variety of co-repressors through the interactions in RD1 and RD2 domains.[1]

Acting as a master negative regulator of neurogenesis, this protein will repress transcription in stem cells and non-neuronal cells by binding a DNA sequence element known as neuron restrictive silencer element. [2]

The fact that transcriptional communication requires high levels of REST during the embryonic development is to avoid terminal differentiation of stem cells into neurons [2]. Depending on the tissue, variations in REST concentrations can result in different diseases, for example, pancreatic cancer cell lines and pancreatic tissue sections showed that the level of REST expressed was elevated according to the degree of cancer development and the higher its concentration the lower the survival rate [3]; on the other hand, in 20% of breast cancer that has normal expression of REST there is a functional deficiency of this protein causing a more aggressive phenotype and poor prognosis. [4]

Knowing the interactions between REST, CoREST and other transcription factors can help us to better understand the mechanism and development of tumors. In this review, various transcription factors that interact with CoREST will be listed and these proteins have an important role in the expression or repression of tumors.

2. Proteins that interact with REST/CoREST complex

Proteins as LSD1, HDAC1, SIN3A and FOXK2 form different complexes with REST and CoREST and they can even interact with each other. These proteins

need to be activated by demethylating repressive histones (LSD1), inositol phosphates (HDAC1), INFs and IL (SIN3A) or by SOX9 (FOXK2) and needs to bind with CoREST to play his role in repression of expression. [5]-[8]

2.1 Lysine Specific Histone Demethylase (LSD1)

Known as KDM1A, AOF2m KIAA0601 or BHC110, is a flavin adenine dinucleotide (FAD), dependent lysine-specific demethylase with monomethyl and dimethyl-histone H3 lysine-4 (H3K4) and H3 lysine-9 (H3K9). As a transcriptional repressor, its erasers the H3K4 methyl mark that is associated with activation of transcription. However, it can also have a gene activating role through demethylating repressive histone marks and possibly non-histone proteins. [9][10]

To accomplish their function LSD1 needs the CoREST repressor to act in the substrate and it's been shown that CoREST provides the specificity in the nucleosome by making contact with the DNA components and positioning LSD1 forming an integral union that can interact and act in the nucleosome.[11]

In Prostate cancer, LSD1 inhibition can markedly decrease Protein Kinase B phosphorylation, known as AKT, this protein has a critical signaling that can regulate cellular function as proliferation, survival, apoptosis, and metabolism which has an important part in oncogenesis. [10][11][12]

2.2 HDAC1

Histone Deacetylase protein have the function of catalyze the acetylation of lysine residues on the N-terminal of the core histones (H2A, H2B, H3, and H4). [13] In the experiments made by Song Y. were demonstrated that LSD1 and HDAC1 work together regulating the architecture of the chromatin, they showed that regulation molecules that activate or inhibit the function of one of them will directly affect the function of the other. [14]

Many isoforms of HDAC are implicated in cancer development and can act as a suppressor or it can lead to up regulation of genes depending on the cell, the target genes and loss in the concentration of HDAC1, 2, 3, 4, and 6 negatively affects proliferation of tumor cells. [15]

The E2F-regulated promotor regulates the transition from G1 to S phase and cyclin E is essential for progression through the G1 phase and initiation of DNA replication. In retinoblastoma the experiments suggest that Retinoblastoma protein (Rb) can recruit HDAC1 and cooperate to suppress the E2F-regulated promoter of the gene encoding the cell-cycle protein cyclin E. [16][17][18]

2.3 SIN3A

The Signal Transducer and Activator of transcription 3 (STAT3) are latent transcription factor that become activated by phosphorylation in respond of interferons, epidermal growth factor, IL-5 and IL-6 acting a in processes as cell growth and apoptosis. Aberrant STAT 3 in breast and prostate cancer, leukemias and lymphomas can lead to malignance transformation through inhibition of apoptosis and the stimulation of growth ensuring tumor survival. [19]

SIN3A acts as a transcriptional repressor working with CoREST and many other proteins. In addition to the regulatory function in cortical neuron differentiation, it's been identified that by forming a complex with HADC1 it can act as a suppressor of STAT3 transcriptional activity. SIN3A directly interacts with STAT3 promoting its deacetylation and nuclear exclusion but his activity depends on the cell and the presence of the cytokines previously mentioned.[7][13]

2.4 FOXK2

Forkhead box K2 FOXK2 is a central transcriptional regulator in embryonic development and cell homeostasis. This protein mediates processes that involve DNA stability and participates in cancer genetics. Although the functional redundancies and non-functional redundancies of FOXK2 still largely unexplored, over the last years experiments has demonstrated that in conjunction with other protein complexes it is directly related to proliferation, differentiation, cell cycle progression, apoptosis, and metabolic reprogramming. [20]

As LSD1 and SIN3A, FOXK2 also actively interact with HDAC1 to regulate transcription. There are two hypothesis that explains the presence of FOXK2 in multiple corepressor complexes, one of them says that interacts with all simultaneously, the other one explains that FOXK2 will interact with certain complexes depending on the cell and under specific cell environment. [21]

In hepatocellular carcinoma FOXK2 knockdown can inhibit the proliferation, colony formation, migration an invasion of HCC cells. There is a possible mechanism where FOXK2 downregulation inhibit Epithelial-Mesenchymal Transition (EMT) which is a cellular program related to malignity in tumors. The hypoxia pathway is a fundamental feature of locally tumors and the repression of FOXK2 leads to depression of this path signaling and promote EMT, an important discovery in the investigation of breast cancer. [22]

3. Conclusion

As mentioned in this review, despite the function in neurogenesis regulation, REST and CoREST role in many complexes that maintain neurological tissues, participate in suppression and expression of cell development, in some cases can be an important factor in some types of cancer. The machinery and the pathway will be determined by the type of tumor,

the tissue that it is located and the type of target cell. Proteins as LSD1, HDAC1, SIN3A and FOXK2 form different types of complexes and have different functions in cell and tumor development, some of which are known, some others are yet to be discovered. The importance of studying these complexes seems to be the best way to better understand cancer physiopathology and to help develop new drugs that can reach these tumors without affecting functional cells.

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