Relationships between CBP and p300 in Epigenetics and Rubinstein-Taybin Syndrome

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Abstract: Rubinstein-Taybi Syndrome (RSTS) is a rare genetic disorder and accounts for one case in every 125,000 to 100,000 cases. It involves poor development of facial features, distal limb abnormalities similar to broaden thumbs and first toes and also mental retardations. RSTS could also extend to other malformations, including neurological and renal malformations. There are many epigenetic mechanisms underlying RSTS. For example, histone acetyltransferases (HATs), histone deacetylases (HDACs) and histone deacetylase inhibitors (HDACI), transcription co-activators. CBP and p300 are enzymes that are encoded by CREB-binding protein (CREBBP) gene and EP300 gene and with these two genes germline mutations, the amount of CBP and p300 could be abnormal, which leads to difficulty in transcription. CBP and p300 are histone acetyltransferases, they are responsible for histone acetylation and increasing gene expression. However, with histone deacetylase, they alter the shape of the chromosome and silence a specific region of the DNA to repress the gene expression. This problem could be solved by histone deacetylase inhibitor. HDACI inhibits HDACs to increase histone acetylation, which then increases gene expression. Nowadays, RSTS mutations could cause tumor growths. It is considered that whether if CBP and p300 as histone acetylases could function to repress tumor development. This paper discusses the underlying epigenetic mechanisms within RSTS and the suitability of using it as a tumor repressor. It is found that CBP could interact with Sam68 and process to prevent tumor formation, which Sam68 is a strong transcription repressor.

1 INTRODUCTION

Rubinstein-Taybi Syndrome (RSTS) is a congenital developmental abnormality characterised by psychomotor delay, facial abnormalities and also relating to cardiac cancers, digestive and skin malformations, especially tumor formations (VanGils et al. 2021, Edward 2017, Boot et al. 2018). This syndrome involves de novo heterozygous mutations within genes and are analyzed mostly from epigenetic aspects.

RSTS is caused by mutations of cAMP response element-binding protein (CREBBP) and E1A-associated protein p300 (EP300) gene. These two genes are responsible for encoding two transcription co-activators and they also act as histone acetyltransferases (HATs), CREB-binding protein (CBP) and p300. CBP and p300 are highly homologous, which they are in the same HATs group (Edward 2017).

Histone acetylation by CBP and p300 could activate gene transcription. However, histone deacetylase (HDACTs) are responsible in silencing genes. Without gene expression, disease like RSTS could occur. Scientists have found a therapeutic method that histone deacetylase inhibitors (HDACI) could inhibit the function of HDACs, which it is responsible for reactivating genes (Edward 2017).

Tumors are associated with RSTS. Nevertheless, the relationship between the phenotypes and genotypes have not be clear (Boot et al. 2018). It is suggested that CBP and p300 as histone acetyltransferase could have the possibility to repress tumor growth by preventing specific gene uncontrolled transcription, which this paper will discuss about. The mechanisms of different elements considering Rubinstein-Taybi Syndrome have been compared. In addition, these mechanisms are tested in theory of repressing tumor development, which in turns could bring another use of CBP and p300.

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2 OVERVIEWS OF RUBINSTEIN-TAYBI SYNDROME

2.1 Symptoms and Phenotypes Considering Rubinstein-Taybi Syndrome (RSTS)

Rubinstein-Taybi Syndrome is a rare congenital genetic disorder characterized by abnormal development of physical features such as short stature, facial abnormalities, broaden thumbs and first toes, however, facial dysmorphism and distal limb abnormalities are reported the most common (Figure 1) (Boot et al. 2018). Facial dysmorphism only occurs to be a feature late in the childhood, owing to the fact that phenotype is evolutionary, and the adult's phenotype could be distinct from the appearance of them as a new born. Broaden thumbs could be a type of distal limb abnormality, although it is not always constant, it is found to be within 69% to 97% of the total RSTS cases (VanGils et al. 2021). In addition, disabilities like psychomotor delays, mental retardations have also been expressed by RSTS patients. RSTS is reported to occur in one case per 100,000 and 125,000 births (Hennekam 2006), and children carrying a pathogenic varient in p300 could cause a pre-eclampsia and hypertension during pregnancy (VanGils et al. 2021). Several malformations are discovered, including cardiac, digestive and skin malformations, also an increasing number of patients have developed benign and malignant tumors, with meningiomas and pilomatricomas the most common (Boot et al. 2018).

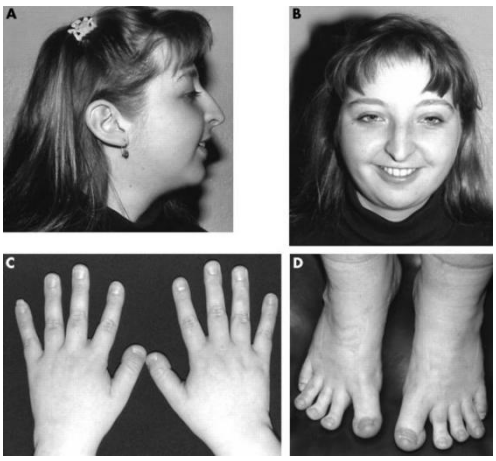

Figure 1: A patient with mild RSTS.

Phenotype like facial dysmorphism with long eyelashes, prominent beaked nose, posteriorly rotated ears and also strabismum are expressed. Figure 1 (A and B) including broadened thumbs and first toes, and broadened terminal phalanges in Figure 1(C and D) (VanGils et al. 2021, Bartsch et al. 2002).

2.2 Genotypes and Causes Associated with Rubinstein-Taybi Syndrome

Rubinstein-Taybi Syndrome is an autosomal dominant trait and caused by de novo heterozygous mutations within the genes that encode the CREB-binding protein (CBP) and EP300 (VanGils et al. 2021, Edward 2017). CREB-binding protein (CREBBP) gene encodes CBP and it is located on chromosome 16p13.3, with this gene germline mutation, it leads to Rubinstein-Taybi Syndrome type I. RSTS I accounts for 50% to 60% of the total RSTS cases and CREBBP gene germline mutation is associated with 106 point mutations and 21 deletions. On the other hand, for Rubinstein-Taybi Syndrome type II, which is caused by E1A-binding protein (EP300 or p300) gene mutation on chromosome 22q13.2 (Boot et al. 2018). RSTS II accounts for approximately 10% of the total RSTS cases. EP300 gene encodes the protein EP300/p300, this gene germline mutation includes 27 point mutations, 6 exonic deletions and 1 whole-gene deletion (Edward 2017). Moreover, severe RSTS could be caused by chromosome 16p13.3 deletion syndrome, and the deleted DNA length expands approximately from 40 kb to >3 Mb (Boot et al. 2018; Bartsch et al. 2006).

3 EPIGENETICS WITHIN RUBINSTEIN-TAYBI SYNDROME

3.1 CBP and p300: Transcription Co-activators

CBP and p300 are highly homologous and are the only two members within the KAT3 family. So most of the missense mutations are sited on the Lysine Acetyltransferase domain (KAT domain) for both CREBBP gene and EP300 gene (VanGils et al. 2021). As CREB-binding protein (CBP) and p300 are transcription co-activators, they interact with KAT domain to activate transcription. Transcription co-activators are proteins that bind with transcription factors to start the transcription process. For example, cAMP response element-binding protein (CREB) as a transcription factor will need to recruit CBP in order to start transcription. This involves interactions

between activation domain of transcription factors and CBP's multiple protein-protein interaction domains, including the transcriptional adaptor zinc-binding (TAZ) domain. The CH1 and CH3 (cysteine-/histidine-rich region) where zinc-binding domains are localized regions regulate most of the CBP's protein-protein interactions (Edward 2017).

It is proposed that the activation of CREB towards its targeted promoters is based on the phosphorylation of CREB by Protein Kinase A (PKA) at Serine-133 in response to advance levels of cAMP. Activation by protein kinase A results in CREB binding with the cAMP response element, because PKA caused CREB phosphorylation, which this action stimulates interactions with many transcription factors and allows it to recruit transcription co-activators, such as CBP. Then CBP can further recruit RNA polymerase II and promot transcription of targeted genes (Everett et al. 2009).

To sum up, CBP as a transcription coactivator is responsible for CREB-dependent transcriptional activation, the interactions between CBP and CREB depends on CREB phosphorylation at Serine 133 located within the kinase-inducible domain (KIK) (Edward 2017). As shown in Figure 2.

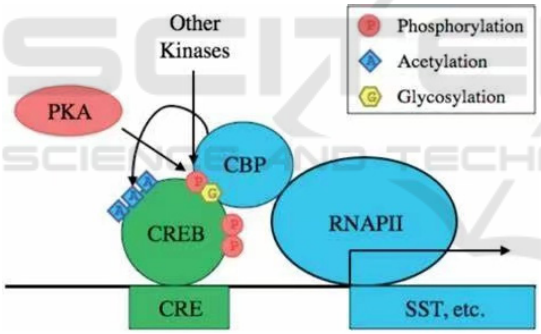

Figure 2: Function of CREB and CBP.

Figure 2 shows protein kinase A causes phosphorylation of the CREB transcription factor and recruit transcription co-activator CREB-binding protein (CBP), which then leads to CBP further recruit RNAPII to activate transcription process (Everett et al. 2009).

3.2 CBP and p300: Histone Acetylation

CREB-binding protein and EP300 are considered histone acetyltransferase (HATs). HATs are enzymes responsible for adding an acetyl group acetyl CoA to the lysine residues on the histone tails and form ε-N-acetyl lysine (Annabelle et al. 2012). Bromodomain could recognize acetylated lysine residues, the KIT11 domain is a lysine acetyltransferase able to transfer acetyl groups on to histone N-terminals (Edward 2017). This process activates transcription by altering the shape of the chromatin via acetylation directly to the histone N-terminal tails of histones H2A, H2B, H3, and H4. This includes H3K14, H3K18, H3K27, and H3K56 shown by Figure 4A and B (Edward 2017). Acetylation by HATs reduces the attractions between the positive histone and the negative DNA, owing to the fact that acetylation decreases the positive charge on the histone and they then developed repulsion. Therefore, the chromatin would be loosen/relaxed. Therefore, RNA polymerase could function to copy information and transcribe.

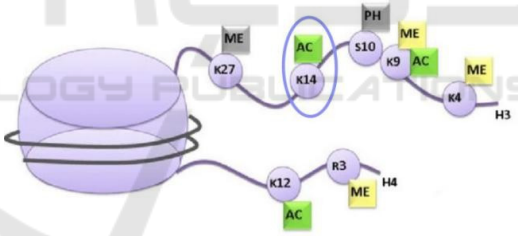

Figure 3: Histone Acetylation.

Figure 3 shows histone acetylation on the lysine residue K14 (H3K14 acetylation) on histone tail.

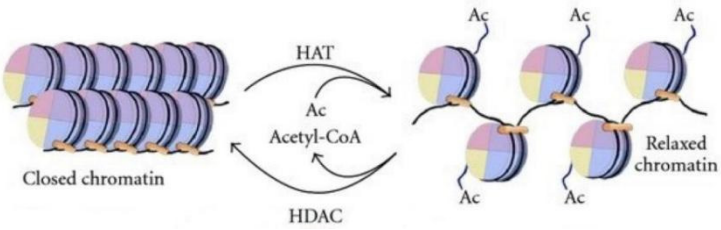

Figure 4: Function of Histone Acetylation.

Acetylation involved in relaxing the structure of the chromosome in order to successfully start the transcription by the RNA polymerase (Annabelle et al. 2012).

4 THERAPEUTIC METHODS FOR RUBINSTEIN-TAYBI SYNDROME

4.1 Histone Deacetylase (HDACs) and Histone Deacetylase Inhibitors (HDI)

Epigenetic mechenisms are reversible, so epigenetic markers can be regulated by Histone acetylation and histone deacetylation by keeping a balance between them. Histone deacetylase (HDACs) are enzymes responsible for removing the acetyl group on the histone tail, in contadiction to the HATs, it increases the positive charge on the histone, causing the negative DNA strand and histone binding more strongly together. This repressed the gene expression by preventing RNA polymerase to assist the forming of mRNA strand. The gene is silenced, which then stops the transcription process.

The statement mentioned above states that mutations within CREB-binding protein gene and EP300 gene germline mutation caused Rubinstein-Taybi Syndrome. To be more specific, deletion of one of the copies of the gene could lead to trancribing an abnormal amount of the normal histone acetylase enzymes. This is thought to be correlated with HDACs causing the gene to be silenced. Shown by Figure 4, the arrow pointing from the right to the left represents HDACs causing the gene the be repressed.

Scientists reported that a whole gene deletion of CREBBP gene and also the truncating mutation was rescued by HDAC inhibitors (Lopez-Atalaya et al. 2012). HDAC inhibitors (HDI) are compounds that inhibits the function of HDACs so that it allows the lysine residues on the histone tails to be acetylased (Figure 5). Some drugs are discovered of having the ability to reactivate silenced genes, such as HDAC inhibitors: SAHA-suberoylanilide, VPA-valporic acid and TSA-trichostatin A (Edward 2017).

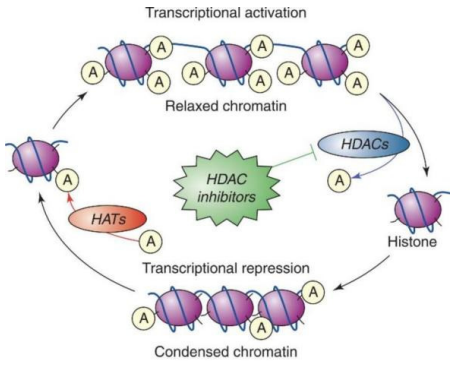

Figure 5: HDAC Inhibitors.

With the help of HDAC inhibitors HDAC will not cause changes to the shape of the chromosome, which means that the gene cannot be silenced.

4.2 Tumors Developed from RSTS

CREBBP and EP300 gene mutations have been found in many benign and malignant tumors (Boot et al. 2018). Nevertheless, the pattern of genotype and phenotype correlation is unclear (Hennekam 2006). It is reported that most of the tumors occur within the head (Miller et al. 1995). They form around parts like large deletion or duplication group, in the groups with nonsense or frameshift mutations, splice site mutations and missense mutations groups (Boot et al. 2018). A total of 115 patients with RSTS, 132 tumors are found, and most are neural crest derived tumors, such as neuroblastoma, meningioma and pheochromocytoma (VanGils et al. 2021).

CBP and p300 are considered cofactors for oncoproteins or for tumor suppressor proteins (VanGils et al. 2021). p53 as an example of tumor suppressor protein binds to a specific region of the DNA and stimulate the production of p21 protein, then p21 interact with cell division-stimulating protein and form a complex to prevent the cell to enter the next stage of cell division (National Center for Biotechnology Information (US), 1998). CBP as transcription cofactor also have tumor suppressing ability. CBP's CH3 domain binds with several viral oncoprotein and Sam68 (a RNA-binding protein). CBP interacts with Sam68, because Sam68 acts as a strong transcription repressor (Hong et al. 2002).

5 CONCLUSIONS

This paper stresses the effect of CBP and p300 responsible for the mechanism of histone acetylation under Rubinstein-Tyabin Syndrome both from the genotype and phenotype aspects. It is discovered that gene germline mutations of the CREB-binding protein (CREBBP) gene and EP300 gene would be a prime factor of causing RSTS, which leads to the improper number of the coded CBP and p300. Gene expression results from histone acetylation, therefore, histone acetyltransferase (HATs) CBP and p300 are responsible for the normal regulating of the genes. However, interactions between histone deacetylase (HDACs) and histone deacetylase inhibitors (HDACI) would regulate gene silencing involved in RSTS. Which then suggests that tumor developments based on gene mutations could be repressed by HATs and HDACs. The uncontrolled cell divisions within

RSTS could be possibly regulated by alternating the epigenetic mechanisms underlying it. For instance, CBP would interact with Sam68 to suppress DNA transcription, therefore, over amount cell division causing a tumor would be controlled. In addition, it is mentioned that the CREBBP gene and EP300 gene mutations had been found in many of the tumors, but the underlying patterns of the genotype and phenotype is unclear. The speculation could be CBP mutation would cause irregular interactions with Sam68 which lead to tumor developments, as it is considered that changes in the structure of a specific transcription coactivator like CBP would alter the binding site with Sam68 to inaccurately repress tumor developments. The ways of repressing tumors might then encourage acknowledging many other transcription factors and inhibitors' functions.

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