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CHANGING LEVELS OF THE PTEN GENE AND ITS PSEUDOGENE PTENP1 IN A CELL CONCERNING DIFFERENT REGULATORY MECHANISMS AND THEIR ROLE FOR A CELL TO BE CANCEROUS OR NON-CANCEROUS

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ABSTRACT

Cancer is a disease, result of different mutations caused in the genes which are regulating cell-growth. As a result of these mutations in the genes, cells are dividing in an uncontrolled manner. Cancer of the breast occurs when it starts in breast cells. Epigenetic, transcriptional, post-transcriptional, and post-translational processes all play roles in controlling PTEN gene expression in cells. Both the PTEN gene (at position q23.3) and the PTENP1 gene (at position p33.3) may be found on chromosome 9. The phosphatase and tensin homolog (PTEN) gene acts as a tumor suppressor. In addition to the processed pseudogene PTENP1 (Phosphatase and Tensin Homolog Pseudogene 1) and PTEN-targeting short noncoding RNAs like microRNAs (miRNAs), PTEN gene expression is controlled by sense and antisense transcripts of the PTENP1 long noncoding RNA. Several transcription factors attach to the PTEN gene promoter in order to activate or inhibit transcription. Some short non-coding RNAS miRNAs regulate PTEN gene expression post-transcriptionally by inhibiting translation at the 3'-untranslated region (3'UTR). Both the PTEN gene and the PTENP1 pseudogene have conserved microRNA binding sites in their 3'UTR sequences. PTENP1 acts as a decoy for miRNA binding, releasing PTEN from miRNA suppression and restoring PTEN's function. Post-translational changes, including as phosphorylation, oxidation, ubiquitination, etc., regulate PTEN stability and activity. We can also regulate the expression of genes epigenetically by recruiting Chromatin Remodelling complexes and many different types of Histone Modifying Enzymes so that some biomolecules can influence the

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expression of genes during particular response at the cellular level and affect the particular cellular physiological response.

***KEYWORDS**: PTEN Gene, PTENP1 Pseudogene, sncRNAs, miRNAs, lncRNAS, Sense and Antisense transcript, Ubiquitination, Epigenetic regulation, Chromatin Remodelling Complexes, Histone Modifying Enzymes.*

I. INTRODUCTION

Cancer is caused when different mutations occur in the genes regulating cell growth. Due to multiple mutations in such types of genes, cells divide in an uncontrolled manner. Breast Cancer is a cancer which develops in breast cells. 'Invasive' and 'Noninvasive' are the terms used to describe the two distinct subtypes of breast cancer. The difference between invasive and noninvasive breast cancer is that the latter spreads beyond the initial tissue, while the former does not. Inhibiting apoptosis and promoting proliferation are only two biological roles played by the PI3K-Akt signalling system, which is negatively regulated by the PTEN tumour suppressor gene (Yang et al., 2016). Because of its biological activity and essential function in PTEN cellular level control, PTENP1, a PTEN pseudogene expressed lncRNA, may also exert a tumour suppressive effect. Several independent gene duplications resulted in the PTEN/ PTENP1 pseudogene. With just 18 nucleotide differences in the coding region, the translation of PTENP1 resulted in non-functional proteins despite its high degree of similarity to the PTEN gene.

A. PTEN and PTENP1 sequence, structure and chromosomal position

On chromosome 9 at position p13.3 lies the PTENP1 gene. On chromosome 10 at locationq23.3 lies the PTEN gene. There is a 1212-nucleotide open reading frame encoded by the nine exons that make up the PTEN gene. The predicted molecular weight of the protein encoded by this gene is 47 kDa (Myers et al., 1998). The protein contains 403 amino acids. The protein PTEN is split into an N-terminal phosphatase catalytic domain and a C-terminal regulatory domain. PTEN has a PI (4,5) P2-binding motif in its N-terminal phosphatase domain. PTEN's substrates are present in the plasma membrane, making the C-terminal lipid-binding C2 domain crucial for membrane localization (Lee et al., 1999).”

II. REGULATION OF PTEN ABUNDANCE AND ACTIVITY

Epigenetic, transcriptional, posttranscriptional, and post-translational mechanisms are essential in regulating PTEN expression in cells. Cancer has been associated with low PTEN levels or activity (Leonardo et al., 2008). These regulatory mechanisms work together to stabilise PTEN levels and activity in normal cells. One of the most fascinating parts of PTEN biology is how it is regulated by its processed pseudogene (PTENP1). “It is imperative to discuss the complex network of interactions between the PTEN gene, PTEN-targeting small noncoding RNAs such as microRNAs (miRNAs), and the sense and antisense transcripts of the PTENP1 long noncoding RNA, all of which regulate PI3K/Akt signalling and play a major role in regulating the pathogenesis of breast cancer (Poliseno et al., 2010).”

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III. TRANSCRIPTIONAL REGULATION OF PTEN

Several transcription factors attach to the PTEN gene promoter in order to activate or inhibit transcription. Examples of such transcription factors include the tumor suppressor genes p53 and early growth response transcription factor 1 (EGR1). The p53 and PTEN genes govern one another's activity through a positive feedback loop (Nakanishi et al., 2014). By connecting to the functional p53 binding site upstream of the PTEN promoter, p53 can upregulate PTEN transcription (Mayo et al., 2002). "PTEN transcription is negatively regulated by the binding of other transcription factors to the PTEN promoter, such as the antisense transcript of the PTEN pseudogene PTENP1(AS) (Guil et al., 2015)."

A. Posttranscriptional regulation of PTEN by miRNA

Current scientific and technological advances in genetics have made considerable strides towards understanding the complexity of noncoding genes and their roles in cellular regulation. These noncoding genes have an outsized impact on gene regulation and play critical roles in developing and managing illness. Association miRNAs, tiny ncRNAs around 14-24 nt in length, influence the PTEN gene post-transcriptionally. These miRNAs prevent the translation of PTEN by binding inside its 3'UTR (He et al., 2010). The miRNA's binding mechanism with the mRNA determines whether a microRNA (miRNA) degrades its target mRNA via perfect complementary synthesis or inhibits translation through imperfect complementary (Dong et al., 2013). Studies have demonstrated that some oncogenic miRNAs may bind to PTEN transcripts and prevent the protein from being translated. This miRNA binding is disease-specific. Increased PTEN-targeting microRNAs have been associated with breast cancer development (Li et al., 2017).

B. Posttranscriptional regulation of PTEN by its pseudogene, PTENP1

Although they cannot create a protein, many pseudogenes are transcribed and operate as decoys for microRNA binding, therefore regulating their coding counterparts (Pink et al., 2011). When acting as microRNA decoys, specific pseudogenes show a tissue-specific pattern of activity, which may allow them to control oncogenes and tumour suppressor genes in a tissue-specific manner (Wu et al., 2017).

PTENP1 pseudogene regulates the PTEN gene post-transcriptionally, creating a new standard for controlling cognate genes. In order to effectively treat cancer, this regulatory process must provide novel therapeutic targets.

The PTENP1 pseudogene generates three transcripts: PTENP1(S), an antisense transcript, and PTENP1(AS), another antisense transcript. The PTENP1(S) sense transcript acts as a sponge in the cytoplasm, soaking up microRNAs that target PTEN. "One of the two antisense PTENP1 transcripts, PTENP1(AS), functions in the nucleus to negatively control PTEN production by attracting the chromatin-remodelling proteins Enhancer of Zeste Homolog 2 and DNA methyltransferase 3a (EZH2) and DNMT3a (DNMT3a) to the PTEN promoter." RNA-RNA interactions between PTENP1(AS) and PTENP1(S) in the cytoplasm improve the sense transcript's miRNA'sponging activity (modified from Guil et al., 2015).

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In order to prevent microRNAs from binding and silencing the PTEN transcript, the sense pseudogene transcript (PTENP1(S)) serves as a sponge or 'decoy' (Poliseno et al., 2010). The most intriguing finding is that microRNA binding sites are conserved between the PTEN gene and the PTENP1 pseudogene in their 3'UTR sequences. Restoring PTEN function, PTENP1 acts as a decoy for miRNA binding and frees PTEN from miRNA suppression (Poliseno et al., 2010).

Additional findings corroborate the PTEN/PTENP1 regulatory cycle by showing that knocking down the PTENP1 pseudogene reduces PTEN mRNA and protein levels (Poliseno et al., 2010). MiRNAs that bind to the S1 region of the three ′ untranslated regions (3′ UTR) of the target mRNA reduce PTEN gene expression. The PTEN protein may be expressed because the transcript of the PTENP1 pseudogene (which has a 3′ UTR with PTEN mRNA) binds to the same miRNAs. The proliferation of cancer cells is therefore inhibited.

C. Post-translational regulation of PTEN

Many post-translational mechanisms control the stability and activity of PTEN. These modifications might include phosphorylation, oxidation, acetylation, ubiquitination, etc.

The PTEN protein is 403 amino acids long and is divided into four PIP2 binding domains, one phosphatase domain with a catalytic core, one C2 domain with known ubiquitination sites, two PEST (proline, glutamic acid, serine, threonine) domains for degradation, and a PDZ interaction motif. “Acylation at protein tyrosine phosphatase (PTPase) and PDZ-binding sites, oxidation, SUMOylation in the C2 domain, and ubiquitination of Lys residues in the PBD and C2 domains are all examples of post-translational regulation of PTEN. Phosphorylation of certain serine and threonine residues in PTEN's C2 domain and C-terminal tail plays a role in PTEN regulation”.

IV. EPIGENETIC REGULATION OF PTEN GENE

Epigenetic changes are the changes produced by altering histones and DNA but without altering the sequence of gene nucleotides. We can upregulate and downregulate the expression of genes by recruiting Chromatin Remodelling Complexes and many different types of Histone Modifying Enzymes. These enzymes regulate the expression of genes epigenetically by phosphorylation, acetylation and methylation of histone proteins resulting in changed expression levels. DNA Methylation also changes the chromatin structure and is associated with transcription repression in vertebrates.

Shanshan et al. (2016) performed a meta-analysis on the clinical and pathological significance of PTEN gene promoter hypermethylation in breast cancer. “We searched PubMed, Embase, Google Scholar, the China National Knowledge Infrastructure, and Web of Science for papers that could be of interest.” Hypermethylation of the PTEN promoter was shown to be substantially higher in DCIS and IDC than in normal breast tissues. A hypermethylated PTEN promoter significantly increased the likelihood of developing DCIS and IDC, according to research published in 2016. Researchers discovered that a high degree of methylation in the PTEN promoter was a strong predictor of breast cancer.

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V. CONCLUSION

Multiple signalling responses occur continually inside a cell, and the cellular physiological responses shift in response to these signals. "Multiple growth factors and hormones transduce their signals inside a cell by binding to their respective receptors on cells, which in turn leads to the production or destruction of a large number of secondary messengers inside the cell, which in turn triggers a chain of cascade reactions that ultimately alters the cellular physiological responses by regulating the expression level of particular genes." To effectively affect the cellular physiological responses that occur during normal signalling, we need biomolecules that can influence the expression of genes during these responses at the cellular level.

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