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Review: Role of NONO Gene from DBHS Complex and its Interaction with PIN1 in Cancer

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Abstract:- Paraspeckle are sub-nuclear bodies found in the interchromatin space of mammalian cells, made from the interaction of non-coding RNA and DBHS (Drosophila behavior human splicing) complex. DBHS consists of p54NRB/NONO, PSPC1, and PSF/SFPQ proteins. Each protein of the DBHS complex contains RRM1/2, NOPS, and the Coiled-coil domain.Amongstthe DBHS complex, NONO protein is involved in breast, prostate, and malignant melanoma progress. NONO gene is engaged in various biological processes, including RNA splicing and editing, DNA unwinding and repairing, and gene transcription. NONO can interact withSFPQ and PSPC1 in the DBHS complex as heterodimers and homodimers. In addition, NONO can also interact with Sterol regulatory-element binding proteins (SREBPs) and stabilize them. (SREBPs) activate genes encoding key enzymes responsible for the biosynthesis of fatty acid and cholesterol in breast cancer. PIN1 and SUPT5H are oncogenic proteins;the function of PIN1 is defined by its two domains: the WW domain and the PPIase domain. NONOand SUPT5H interact withthe WW domain of the PIN1 protein, which induces the PPIase domain and promotes cancer. PIN1 stabilizes the NONO, and SUPT5H, contributing to breast cancer cell proliferation, migration, invasion, cell cycle, and apoptosis. Silencing NONO, PIN1, and SUPT5H can suppress tumor growth and be a good target for therapeutic purposes.

Keywords:- *NONO gene, DBHS Complex, PIN1, Cancer.*

I. INTRODUCTION

We focused on the functional interaction of Non-POU Domain-Containing Octamer-Binding(NONO) and DBHS complex proteinand their correlation with cancer and interaction with PIN1. Paraspeckles are nuclease bodies consisting of one non-coding RNA and a combination of DBHSproteins. DBHSis a family of three different proteins involved in distinct functions, NONO,PSPC1, and SFP[1].DBHS proteins as multifunctional nuclear proteins implicatedin subnuclear body formation,co-activation, transcription initiation[2][3]corepression, constitutive and alternative splicing[4][5][6][7] transcriptionaltermination[8] DNA repair[9], contributing to circadian rhythm regulation [10][11], tumor suppression [12] and Drosophila behavior [13].From the DBHS complex,splicing factor proline and glutamine-rich (SFPQ) and NONO are highlyplentifuland expressed in various cell lines and tissues [9]. DBHS proteins are essential for forming subnuclear paraspeckles[14].Crystallography results show that PSPC1 residues (61-32) and NONO residues(53-312) include a partial DBHS domain; it contains two RNA-recognition motifs (RRM) domains, the NONA/paraspeckle domain (NOPS) domain and part of the coiled-coil domain [15].Each unit of DBHS protein has multiple binding domains which bind to a specific target. For NONO protein, these domains consist of n-terminal G-rich amino acid followed by RRM1,RRM2,NOPS,COILED-COIL,domain and finally ending by GP-rich amino acid[16], [17].The same lineup of domains is repeated for PSPC1 and SFPQproteins; however, they are different at the start and end points[15]. PSPC1 has often been used as a paraspeckles marker[1].Inthe DBHS complex,PSPC1 is much less abundant than SFPQ, thus, knocking down pspc1 does not affect theparaspeckle complexwithin the Hela cell. For the integrity and function of paraspeckles, the interaction between NONO and PSPC1 is crucial[18][19]. pspc1 makes interaction with NONO via the coiled-coil domain.The pspc1 and NONO heterodimersare essential structural components of paraspeckles, where NONO and pspc1 proteins have more than 70% sequence identity.PSPC1 and NONOhave dynamic processes that can readily exchange interaction partners to form dimerization states and change their function.This alteration is dependent on cell expression,for example,mouse Sertolicellshave high expression of SFPQ and PSPC1 compared to NONO, in contrast HeLacellsNONO and SFPQ are more abundant than PSPC1[17].All three DBHS members,NONO, PSPC1, and SFPQ, have 2 tandem RNA recognition motifs (RRMs) that show more than 50% sequence identity [20]. RRMs motif domain of pspc1-protein is used to target paraspeckle [1].

II. NONO PROTEIN STABILITY REGULATED BY PIN1

NONO is known as nuclear RNA- and DNA-binding protein which is a multifunctional DBHS (Drosophila behavior/human splicing) protein defined by N-terminal RNA recognition motifs (RRMs), protein-protein interaction NONA/paraspeckle domain (NOPS), and a C-terminal coiled-coil domain [21][22]. NONO protein is mainly found in the nucleus, particularly in paraspeckles [23][8], whichis involved in every step of gene regulation: repression and transcriptional activation[24], termination of transcription, RNA transport[25], pre-mRNA splicing[24][26] and nuclear retention of defective RNA

for editing [27][5]. It has shown that NONO's interaction with splicing factor proline and glutamine-rich (SFPQ) regulates the DNA repair mechanism[28]. Because NONO plays a significant role in multiple processes, it is dysregulated in many cancers. For example,in breast cancer, the expression of NONO promotes the transcriptional activation of lipogenic genes and lipid production by interacting with and stabilizing the sterol regulatory element-binding protein 1 (SREBP1) [29]. In hepatocarcinoma, NONO contributes to carcinogenesis via oncogenic splicing of BIN1 protein.The BIN1 protein is involved in endocytosis and the self-destruction of cells (apoptosis)[30]. NONO is robustly expressed in prostate cancers, and promotes castration-resistant prostate cancer development by causing differential EPHA6 splicing [31][32]. Additionally, NONO expression is remarkably raised in Esophageal squamous cell carcinomaand melanoma[33],and gastric cancer cells [34], and the increased expression of NONO is associated with the aggressiveness of cancers. Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (PIN1) regulates the conformational changes of pSer/Thr-Pro motifs and causes the change in the function, structure, or stability of various proteins[35][36]. Studies have revealed overexpression of PIN1 speeds up genomic instability and promote tumorigenesis by disrupting cell cycle coordination [37]. PIN1 is commonly dysregulated in various cancer, and its overexpression and/or overactivation is linked to a poor clinical prognosis [38], [39]. Overactivation of PIN1 agitatesthe balance between oncogenic and tumor-suppressing proteins, moving it towards oncogenesis; expected that more than 40 oncogenes are activated, and over 20 tumor suppressors are inactivated in numerous cancers [40]. NONO is ranked among the top proteins with similar functions to peptidylprolyl (PIN1) [41].

III. NONO INTERACTS WITH PIN1 ON ITS N-TERMINAL (WW) DOMAIN

PIN1, which is an oncoprotein, its function defined by its two domains: WW domain and PPIase domain. It has been demonstrated that the WW domain has a stronger affinity for its substrate than the PPIase domain[42] and the binding of the WW domain with the substrate enables PIN1 to perform molecular functions via the PPIase domain [43]. It is determined that PIN1 promotes the stability of NONO protein by binding at the WW domain and preventing proteasomal degradation of NONO[44].

IV. SUPT5H AND PIN1 INTERACTION IN BREAST CANCER

Aberrant expression of PIN1 is associated with the wider signaling network's distortions that fuel cancer progression. In cancers, overactivation of PIN1 is associated with poor patient survival. Because silencing of PIN1 is associated with the inhibition of breast cancer cell proliferation and tumorigenesis of breast cancer stem cells, molecular therapy for targeting PIN1 is growing [45][46]. SUPT5H is ranked among the top-ranked protein with identical functions to peptidylprolyl cis/trans isomerase (PIN1). PIN1 is a 163 residue protein containing the N-terminal WW and C-terminal PPIase domains. Studies show that the PINNONO1 WW domain physically interacts with SUPT5H protein. PIN1 stabilizes SUPT5H and has a positive correlation[47]. SUPT5H contributes to breast cancer cell proliferation, cell cycle, invasion, migration, and apoptosis. A study revealed that the oncogenic function of SUPT5H could be a potential therapeutic target of interest to counter breast cancer [47].

V. NONO STABILES LIPID METABOLISM IN BREAST CANCER

NONO is highly expressed, approximately 63% of breast cancer[29]. Sterol regulatory-element binding proteins (SREBPs) family, including SREBP-1a, SREBP-1c, and SREBP-2 in mammalian cells, can activate the transcription of genes encoding key enzymes responsible for the biosynthesis of fatty acid and cholesterol [29]. SREBPs are master transcription factors that control lipid metabolism[48]. Studies show that endogenous NONO is associated with endogenous nSREBP-a1 in HEK293T cells; this was approved by co-transfection of the Cell with NONO-GFP and nSREBP-a1-charry, where prominent yellow color in the microscopic overlay images was detected suggesting that these two proteins interact and demonstrate physical interaction with each other. It was also shown that the conserved Y267 residue of NONO is essential for binding to the SREBP-a1 protein. This conserved Y267 residue plays a considerable role in interaction with PSPC-1 too. NONO regulates the abundance of nSREBP-1a; interestingly, overexpression of NONO-WT in HEK293T cells resulted in a significant accumulation of endogenous nSREPB-1 protein.

Conversely, knockdown of the NONO gene with specific siRNA within MCF-7, Hela cancer cells had no effects on the mRNA levels of SREBP-1a but decreased the nSREBP-1 protein. Therefore, NONO gives stability to the nSREBP-1 at the protein level [29]. NONO-WT was treated with cycloheximide, an inhibitor of protein synthesis, to examine the degradation rate of nSREBP-1, showing that degradation is significantly slower in a cell transfected with NONO-WT as compared with those transfected with vector. It is well-known that nSREBP-1a proteins are degraded through the ubiquitination-proteasome mechanism. Still, in the cancer cell, the degradation of nSREBP-1a is slow or not, which takes stability from NONO protein. Knockdown of NONO in HEK293T cells caused significantly increased ubiquitination in the over-expressed nSERBP-1a protein [29]. SREBP-1 expression is correlated with tumor size in human breast cancer-triggered tumors[48]. It was found by knockdown of the NONO gene that the lipped droplet in MCF-7 cells was decreased [29]. NONO binding to nSREBP-1a is required for SREBP-1a-dependent lipogenic gene expression. NONO promotes breast cancer cell proliferation and tumor growth through SREBP-1a. Knockdown of NONO inhibits the growth of MCF-7; however, knockdown of DBHS protein does not affect the growth of MCF-7 cells.

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VI. NONO/P54 NRBAND PSPC-1 STRUCTURE IN DBHS COMPLEX

70% of domain sequences of NONO and PSPC-1 are similar; each of them has four domains for binding to RNA/DNA and protein; from the n-terminal, the domain has started in NONO from G-rich, RRM1(118-187), RRM2 (188-316), NOPS (268-316), Coiled-coil (317-375), and GP-rich .and for PSPC-1 from n-terminal; AP-rich, RRM1 (84-154), RRM2 (155-234), NOPS (235-283), COILED-COIL (284-381). NONO is found in the nucleus of most mammalian cells and is primarily distributed within the nucleolus. NONO gene location is on the plus strand of the X-chromosome [49]. It can also be concentrated within sub-nuclear domains known as paraspeckles [50]. NONO has also been observed within the brain, localized in the cytoplasm of hippocampal neurons associated with RNA transport granules[49].

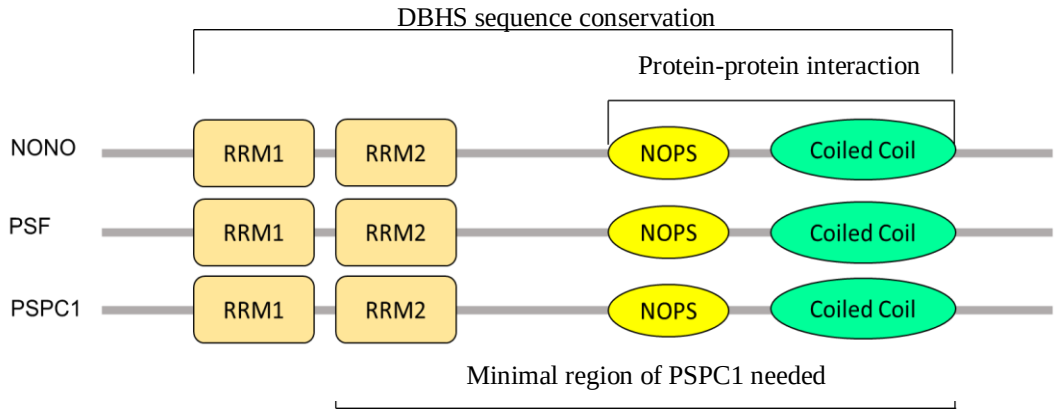

Fig. 1: The DBHS protein family shows domain structure and indicates regions involved in paraspeckle biology

VII. ROLES OF DBHSIN TRANSCRIPTIONAL REGULATION AND REPRESSION

DBHS proteins mediate transcriptional regulation and repression[16][20]. DBHS proteins associate synergistically with several transcription factors, DNA and RNA, acting bifunctionally as positive and negative transcriptional regulators. Thus, as with many transcription factors, their precise role is context-dependent[51]. The DBHS family complex act as a repressor and appears primarily driven by and dependent on SFPQ, either in a homodimer or heterodimer context. Studies have shown that SFPQ binds directly to the target gene promoter and recruits silencers such as Sin3A and HDAC[52][3]SFPQ/NONO can act on hormone receptors such as thyroid and retinoid X receptors [53] or, in complex with steroidogenic factor 1, repress the human CYP17 gene or gene involved in circadian rhythms [54][55]. SFPQ/NONO can also negatively regulate transcription by sequestering activators away from the target gene promoter. For example, direct binding of SFPQ/NONO to the progesterone receptor can prevent its binding to DNA [3].

VIII. POST-TRANSLATIONAL MODIFICATION OF DBHS

DBHS are substrates for several post-translational modifications. NONO is phosphorylated in the region proximal to the coiled-coil domain during mitosis; thus, phosphorylation of the motif region provides a binding site for PIN1 that may lead to subsequent conformational changes in this region. NONO N-terminal is also phosphorylated by CDK1 during mitosis for RNA binding to simple substrates in vitro; also, N-terminus 53 residues of NONO may allosterically regulate RNA-binding ability. In addition, NONO is a substrate for protein phosphates, which associates with NONO RRM1 and influences NONO post-translation splicing[49].

IX. SILENCING THE NONO GENE CAN AFFECT CANCER CELL VIABILITY AND CELL CYCLE

Silencing of NONO gene expression decreases cell viability and colony-forming ability, induces apoptosis, promotes mitochondrial membrane potential changes, and reduces breast cancer cells' migratory and invasive potentials. It was demonstrated that siRNA-NONO efficiently reduced the mRNA and protein levels of the NONO gene in both MDA-MB-231 and MCF-7 cells[44]. Knockdown of the NONO gene affected on cell cycle as analyzed by flow cytometry. Knockdown of NONO in MDA-MD231 and MCF-7cell significantly arrests Cell at the S-phase of the cell cycle, at the same time, decrease the percentage of cells in the G2/M phase in the case of MDA-MB-231 and G0/G1 and G2/M phase in MCF-7 cells [44].

A. Therapeutic Targets

Mutations and dysfunction in genes are the dominant reason for the increased number of cancer cases. In the case of cancer healing, chemotherapy mechanisms are prominently used; however, targeting the specific oncologic gene by modern genome editing techniques can be a potential therapeutic approach. NONO, PIN1, and SUPT5 were significant for cancer growth, and they could be potential targets and markers for chemotherapy and gene therapy mechanisms for suppressing cancer cells [44][47]

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B. Future Perspective

DBHS proteins as multifunctional nuclear proteins implicated in subnuclear body formation, co-activation, transcription initiation[2], and corepression; constitutive and alternative splicing [4]transcriptional termination[8] and DNA repair[9]. And tumor suppression[12]. DBHS complex consists of NONO, PSPC1, and SFPQ proteins, each of which has a different domain. NONO gene was found to develop breast cancer [17], prostate cancer [19], and hepatic cancer [46). NONO gene is involved in various processes, including RNA splicing and editing, DNA unwinding and repairing, and gene transcription. Structurally, p54nrb(NONO) contains several defined domains, including RNA recognition motif domains, DNA binding domain, and a coiled-coil domain, And is involved in multifunction Beyond the interaction of NONO with paraspeckle and also interacts with PIN1 protein. Overexpression and overactivation of PIN1 accelerate genomic instability, promotes tumorigenesis by disrupting cell cycle coordination, and disrupt the balance between oncogenic and tumor-suppressing proteins, moving it towards oncogenesis; more than 40 oncogenes are activated, and over 20 tumor suppressors are inactivated in numerous cancers[40][38]. The essential role of these proteins in tumor growth is unknown. PIN1 oncoprotein is defined by its two domains: WW and PPIase domains. The NONO gene was intercted into the WW domain of PIN1 to stabilize the NONO protein. At the same time, other oncogenic proteins SUPT5H also interactedwith the WW domain of PIN1 to stabilize the SUPT5H, which has a significant role in tumor progression. Here is a question how does the PIN1 protein interactwith NONO and SUPT5Hin the same domain? Does it any competition between NONO and SUPT5H, and how are both proteins regulated by the PIN1 protein? IndeedDBHS complex proteins are found, as a hetero-dimer or alone, in several nuclear complexes involved in the binding and processing of nucleic acids. How are these multifunctional proteins operating in the simultaneous processes occurring in the cell nucleus? Due to their dual RNA/DNA-binding properties and the ability to interact with several protein counterparts, these proteins might be regarded as ‘sticky’ proteins that can link multiple nuclear processes. Silencing NONO, PIN1, and SUPT5H genes suppressed the tumor's growth, indicating that these proteins will be therapeutic targets and markers for the cancerous Cell.

X. RESULT

These paraspeckle nuclear bodies are complex of three proteins, and a non-coding RNA is involved in many interaction types.DBHSconsists of three proteins: NONO, PSPC1,and FSP;these proteinshavea specific multidomain for binding to proteins and RNA/DNA. DBHSproteins as multifunctional nuclear proteins implicated in subnuclear body formation; co-activation, transcription initiation[2][3] and corepression; constitutive and alternative splicing[4][5][6][7] transcriptional termination[8] and DNA repairamong this three protein which more has involved or to distinct interactionare NONO, pspc1 such as transcription factor,polymerase, nuclear-receptor,and gene regulation transcriptional regulation, RNA processing,transport DNA repair mechanism, or controlling gene expression during many cellular processes including differentiation stress responses.In most cancerous cases, the expression of NONO and related proteins will increase, such as in breast cancerand malignant melanoma. NONO interactsand gives stability to nSREBP-a1,which the SREBP(sterol regulatory element-binding protein) is the protein that regulates lipogenic genes and cholesterol biosynthetic genes.NONO regulates the abundance of nSREBP-1a; interestingly,overexpression of NONO-WT in HEK293T cells resulted in a significant accumulation of endogenous nSREPB-1 protein.NONO werintrect homo, heterodimer to SFPQ, PSPC1. PIN1 and SUPT5H are oncogenic proteins, NONOand SUPT5H are both interact to WW domain of PIN1 protein, which PIN1 stabilized the NONO and SUPT5H protein. Silencing of NONO,PIN1, and SUPT5H were demonstrated the significant decrease of tumor growths.

XI. CONCLUSION

Paraspeckle are sub-nuclear bodies found in the interchromatin space of mammalian cells, made from the interaction of non-coding RNA and DBHS (Drosophila behavior human splicing) complex. DBHS, a multifunctional complex, consists of three proteins: NONO, PSPC1, and FSP; these proteins have a specific multidomain for binding to proteins and RNA/DNA. NONO gene plays a crucial role in cancer progression by involving various biological processes, including RNA splicing and editing, DNA unwinding and repairing, and gene transcription. NONO can interact with SFPQ and PSPC1 in the DBHS complex. In addition, NONO can also interact with(SREBPs) and stabilize them. (SREBPs) activate genes encoding key enzymes responsible for the biosynthesis of fatty acid and cholesterol in breast cancer. PIN1 and SUPT5H are oncogenic proteins where PIN1 interacts and stabilizes the NONO, and SUPT5H, contributing to breast cancer cell proliferation, migration, invasion, cell cycle, and apoptosis. Silencing NONO, PIN1 and SUPT5H were shown to decrease tumor growth significantly, and they can be a good target for therapeutic purposes.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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