

RESEARCH ARTICLE

ROLE OF R2TP COMPLEX IN LYMPHOMA AND ITS THERAPEUTIC POTENTIAL

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Abstract

..... The R2TP complex which comprises of RUVBL1, RUVBL2, PIH1D1 and RPAP3 in humans is known to be a specialized Co-chaperone of Hsp-90 protein. This multimeric-protein complex is involved in the assembly and maturation of several multi-subunit complexes including RNA polymerase II, small nucleolar ribonucleoproteins, and complexes containing phosphatidylinositol-3-kinase-like kinases. Since their discovery as a co-chaperone of Hsp90, the R2TP complex is involved in multitude of cellular processes including, chromatin remodelling, transcription regulation, ribonucleoprotein complex biogenesis, mitotic assembly, telomerase complex assembly, and apoptosis. Lymphoma arises from the abnormal proliferation of B-cells and the R2TP complex have been reported to play an important role in the activation of p53 and RB. Therefore, the inactivation in any of the tumor suppressor pathways can drive cells to malignancy. However, there are multiple factors which may contribute towards malignancy but the folding defects in these tumor suppressor pathways could be one of the reasons. R2TP is tightly linked with oncogenesis and its inhibition can decrease the proliferation activity of cancer cells. So, the multisubunit chaperone complex as well as its components could be promising candidates for cancer chemotherapy.

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Introduction:-

Lymphomas are heterogenous group of disorders which accounts for up to 3% of all malignancies. The estimated incidence of non-Hodgkin's lymphoma (NHL), according to Globocan (2012) is 5/100,000 (3,85,741 new cases), with mortality rate of 2.5/100,000 (1,99,630 deaths) worldwide(1). B-cell non-Hodgkin lymphoma make up 80-85% of all NHLs in India(2–4). The most common subtype is diffuse large B-cell lymphoma (**DLBCL**)accounting (60%) followed by indolent lymphoma (12-20%) in India. While the rate of occurrence of the NHL is relatively smaller in India than in the developed countries however the rate of mortality is almost same. According the 2012 Globocan data the mortality to incidence ration in India is 69.7%(1).This represents the poor overall 5-year survival below the global average. Clinical models are also used to classify high-risk patients whoundergo empirical treatment, despite developments in the molecular understanding of DLBCL pathogenesis(2).

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Address:- Department of Biochemistry, Teaching block 3rd floor, AIIMS, Ansari Nagar-110029. Email: riyaz978@gmail.com Diffuse large B-cell lymphoma (DLBCL) is an aggressive malignancy of mature B lymphocytes. It is the most common non-Hodgkin's lymphoma in adults with heterogenous genetic and clinical disorders. DLBCL originates primarily from the B-cells of the germinal centre (GC). The two major hallmarks of the cancer are high growth rate and genomic instability(3). The rapid rate of proliferation predisposes normal cells of GCB cells into malignant conversion(4). Increased cellular proliferation has been shown to be associated with adverse DLBCL outcomes. The components of the cell cycle and its regulators are stated to be disrupted in number of DLBCLs. The most important biochemical mechanism responsible for rapid proliferation and transformation are deregulations of tumor suppressor pathways like p53 and pRb(5,6). The novel mechanism of Rb and p53 activation by R2TP complex have been recently suggested and therefore the alteration in any component of this co-chaperone can drive cells to malignancy.

For the inactivation of these tumor suppressor pathways several mechanisms have been proposed, such as inactivation of p16 for pRB, cyclin overexpression, phosphatase overexpression, genome level mutation and degradation(7,8). In addition to these mechanisms there are variety of tumors where all these pathways are normal but still pRB and p53 is non-functional and the explanation for this inactivation of tumor suppressor pathways can lie on their folding defects. Chaperones the machinery dedicated for folding plays an important role in preserving cellular proteostasis. It has been suspected that a recently discovered R2TP complex plays a role in p53 folding and tetramerization(9,10).

The R2TP complex is known to be the master regulator of cell growth and survival(10). This complex is involved in the assembly of large protein or protein-RNA complexes such as RNA polymerase, small nucleolar ribonucleoprotein (SnoRNPs), phosphatidylinositol 3-kinase related kinases (PIKKs), and their complexes(11). Four core proteins comprise the R2TP complex: RUVBL1, RUVBL2,PIH1D1, and RPAP3. RPAP3 has two repeats of tetratricopeptide (TPR) binding to Hsp90. Direct association of PIH1D1 with RPAP3 inhibit the ATPase activity of Hsp90 and promote client protein loading. The essential ATPases of the AAA+ super-family are RUVBL1 and RUVBL2(11). AAA+ ATPases usually act as hexamers and they hydrolyze ATP to create a force that can be used to remodel either proteins or nucleic acids. RUVBL1/2 binds both nucleic acids and proteins howbeit the molecular role remains elusive(10). The recent data suggests that the Hsp90/R2TP system is a molecular machine devoted to the assembly of multi-molecular protein complexes with an intriguing role for cell signalling machineries(10). The recently discovered human Ecdysoneless (ECD) has been found to be a part of R2TP complex which serve as a bridge between the R2TP complex and tumour suppressor protein pRB(12). Its noteworthy that p53 has already been shown to be stabilized by R2TP complex (9). Some studies have shown that pRB is overexpressed in majority of the malignant lymphomas(13).

R2TP directly interacts with Nop58 and dyskerin, a component of box C/D and box H/ACA snoRNP. In cancer cells, some of the R2TP and snoRNP components as well as many snoRNAs are upregulated to enhance the snoRNP synthesis to process the pre-rRNA efficiently and to produce high amount of ribosome. This elevated snoRNP and ribosome biogenesis negatively regulates the tumor suppressor p53 and that triggers tumorigenesis, whereas inhibition of the snoRNP synthesis in cancer cells induces ribosome stress, which activates p53 and inhibits cell proliferation. To downregulate the highly activated snoRNP/ribosome biogenesis in cancer cells, inhibition of the ATPase activity of R2TP and/or blocking its interaction with Nop58, and dyskerin could be considered a promising therapeutic approach. Thus, R2TP has great potential as a drug target for future cancer therapeutic research and development(14).

Small molecules that block the PIH-N phosphopeptide binding domain by mimicking the DpSDD motif would be predicted to prevent the RT2P complex from recognizing its substrates. Notably, the PIH1D1 subunit is overexpressed in several breast cancer cell lines, which may reflect a dependency of the tumor growth for R2TP complex activity. Therefore, it is possible that inhibitors of PIH-N domain interactions could be used as an anticancer therapeutic for tumors that are over reliant on such chaperone activities. It suggests that PIH1D1 may have an important role in mTORC1 regulation in breast cancers(15).Most of the currently known complexes needing the action of R2TP/PFLD have been found deregulated in cancer(16).Amphiregulin, an EGFR ligand, as a target of WD repeat protein Monad, a component of R2TP/prefoldin-like complex, in MDA-MB-231 breast cancer cells. Monad specifically interacted with both the 3'-UTR of amphiregulin mRNA and the RNA degrading exosome, and enhanced decay of amphiregulin transcripts. Knockdown of Monad increased invasion and this effect was abolished with anti-amphiregulin neutralizing antibody. These results suggest that Monad could prevent amphiregulin-mediated invasion by degrading amphiregulin mRNA(17).

PDRG1 is an understudied protein of the R2TP/prefoldin-like complex that has been found as part of different multiprotein complexes. Increased PDRG1 expression levels have been associated with several types of tumors that concomitantly show global DNA hypomethylation. More recently, this protein has been uncovered as an interaction target for methionine adenosyl-transferase catalytic subunits MATa1 and MATa2. Through this interaction, PDRG1 downregulates nuclear S-adenosylmethionine synthesis, hence impacting epigenetic methylations(18).RPAP3 isoform 1, but not isoform 2, interacts with PIH1D1 for its stabilization probably due to the protection from its degradation. Elucidation of the mechanism by which RPAP3 isoform 2 reduces the cell survival pathway may provide approaches for the treatment of cancer(19).

PIKKs are key signal transducers that are involved in diverse cellular processes such as nutrient signalling, DNA damage response, mRNA surveillance pathway as well as chromatin remodelling. It has been identified that PAQosome is required for the stability of PIKK complexes through interacting with TELO2 (Telomere maintenance 2), which is a HEAT-repeat containing protein.mTOR is involved in many cellular processes including protein, lipid and nucleotide synthesis, and autophagy. It has been identified that PIH1D1 specifically interacts with mTORC1 but not with mTORC2, and its interaction is required for mTORC1 activity. Given that mTOR protein stability is maintained by R2TP/PAQosome association through TELO2, high levels of R2TP might stabilize overexpressed-mTOR and contribute to the malignancy of cancer. Given that R2TP/PAQosome are involved in DDR through ATM/ATR, it could progress this hyperactive ATR-Chk1 pathway in ATMdeficient cells. R2TP/PAQosome contributes to cancer progression through activating snoRNP biogenesis.

Conclusion:-

The functionality of R2TP assisting HSP90 in the assembly of protein complexes is still poorly understood. The role of prefoldin/like proteins in the complex is still obscure. RUVBL1 and RUVBL2 are associated to several other cellular complexes and it has not been formally demonstrated that their oncogenic activity is related to their function within the R2TP chaperone. Future research into the PIKKs will surely help us to understand not only how cells maintain genome integrity to prevent diseases such as cancer but, on their regulation, and activities, possibly drug developments too. Studies are also needed to elucidate the role of the R2TP complex in the stepwise assembly of the box C/D snoRNP and box H/ACA snoRNPs. R2TP/PAQosome is tightly linked with oncogenesis, and its inhibition could decrease proliferation activity of the cancer cells. To downregulate the highly activated snoRNP/ribosome biogenesis in cancer cells, inhibition of the ATPase activity of R2TP and/or blocking its interaction with Nop58, and dyskerin could be considered a promising therapeutic approach. Therefore, the multisubunit chaperone complex as well as its components could be promising candidates for cancer chemotherapy.

Conflict of interest:

None declared.

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