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Sequence-Structure Relationship Guided Comparative Analysis of DEPDC1A and DEDC1B, Cancer Related Proteins

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Abstract: *Cancer is one of the most widely, studied multifaceted disease, involving a number of proteins which are differentially expressed in the tumor cells when compared to that of normal healthy cells. One such protein is DEP domain containing protein 1, which is expressed as two forms DEPDC1A and DEPDC1B. The two proteins have been found to be overexpressed in various type of cancers, making them a therapeutic target. However, to develop a more effective and disease specific drug, it is important to have a better understanding of the structural and functional characteristics of the target proteins, namely, DEPDC1A and DEPDC1B. The present study focuses on identifying the structural similarities/ dissimilarities between the two proteins and relating the observed results to their functional aspect.*

Keywords: *Oral Cancer; DEPDC1A; DEPDC1B; Potential Biomarkers*

Abbreviations: *DEPDC1: DEP domain containing protein 1; DEPDC1A: DEP domain containing protein 1A; DEPDC1B: DEP domain containing protein 1B; FA: Focal Adhesion; PTPRF: Focal Adhesion associated Protein Tyrosine Phosphatase Receptor Type F*

1. INTRODUCTION

Cancer, one of the most widely studied multifaceted disease, involves irregular growth and proliferation of the cells with a potential of metastasizing to other body parts [1], owing to an increased oncogene function, loss of function of several tumor suppressor genes resulting in unusual regulation of cell cycle [2]. Cancer is associated with alterations in a diverse number intracellular pathways, thereby leading to a transformed tumor cell metabolism and differential expression of a wide array of proteins, and enhancing the survival rate and growth of the tumor cell [3]. One such novel protein, often found to be differentially expressed in a number of cancers is, DEPDC1 i.e. DEP domain containing 1 protein. For instance, a study in the year 2007 reported over expression of DEPDC1 in the bladder cancer cells in comparison with 24 normal/ control human tissue and established via northern blot as well as immune-histochemical assays [4]. Another study in the year 2014, reported over expression of the protein DEPDC1B (DEP domain containing protein 1B), in oral cancer patients, where in it was observed that DEPDC1B mediates its function of cell migration as well as invasion, upon its interaction with another protein Rac1 [5]. Apart from stimulating Rac1 activation followed by cell proliferation [6], DEPDC1B has shown to play a crucial role in directing the de-adhesion events followed by cell cycle progression during mitosis. The study reported that DEPDC1B upon its accumulation in G2 phase of the cell cycle, competes with RhoA for its binding with 'Focal Adhesion (FA) associated protein tyrosine phosphatase receptor type F (PTPRF)' and induces the disassembling of Focal adhesions (FAs) leading to the morphological changes important for mitotic entry [7], indicating that its overexpression might enhance the cell cycle progression leading to carcinogenesis. Also, a study conducted in the year 2013, observed the role of DEPDC1B paralog, DEPDC1A in multiple myeloma, where in increased expression of the protein in malignant plasma cells lead to low survival rate in patients and knockdown of DEPDC1A protein hindered human myeloma cell line growth [8].

Structurally, DEPDC1B comprises of two conserved domains, namely DEP, a 90 amino acid long globular domain initially discovered in three proteins: Drosophila disheveled, EGL-10 of Caenorhabditis elegans and mammalian Pleckstrin, and RhoGAP [9-11]. The DEP domain is known

to facilitate the interaction between DEPDC1B and G-protein coupled receptor and the membrane phospholipids, essential for Wnt mediated signaling pathway and RhoGAP domain mediates the Rho GTPase signaling pathway [12-14]. However, not much is known about the structural as well as functional features of the DEPDC1B paralog, DEPDC1A, a poorly characterized protein with only a few published studies, for instance, it has been reported as a poor prognostic marker in breast, bladder, lung cancer and more recently in multiple myeloma [8, 15-17]

With both the proteins being involved directly or indirectly in tumorigenesis, it becomes important to have a better understand of the structural similarities and dissimilarities between DEPDC1A and DEPDC1B, and the influence of structural differences on their functional aspect. Also, the differential expression of the two proteins in the tumor cells when compared to the normal healthy cells, indicate the prominence of DEPDC1A and DEPDC1B as a potential protein based biomarker and an efficient diagnostic, prognostic and therapeutic purposes. The present study therefore, focuses on comparing the secondary structure of the two proteins and relating the observed differences/ similarities to their functional aspect.

2. METHODOLOGY

2.1 Retrieval of Protein Sequences

The protein sequences of the proteins DEPDC1A (UniProt ID: Q5TB30) and DEPDC1B (UniProt ID: Q8WUY9) was downloaded in FASTA format from UniProt (http://www.uniprot.org/) [18].

2.2 Pairwise Sequence Alignment of the Protein Sequences

The retrieval of the respective protein sequences was followed by the alignment of the two sequences using the software EMBOSS needle (http://www.ebi.ac.uk/Tools/psa/emboss_needle/) [19], in order to identify the similarities/ dissimilarities between the sequences.

2.3 Prediction of Secondary Structure

The secondary structure of the two proteins were predicted using GOR IV (https://npsa-prabi.ibcp.fr/cgi-bin/npsa_automat.pl?page=npsa_gor4.html) [20], a secondary structure prediction server, followed by their comparison in order to understand the structural dissimilarities that might have occurred due to differences in their protein sequences.

2.4 Identification of Domain/motif

PROSITE (http://prosite.expasy.org/) [21], a server for analyzing and identifying the domain/motif in a protein, was used to identify the PROSITE domain in the proteins, DEPDC1A and DEPDC1B.

2.5 Comparative Analysis of the DEP Domain Protein Sequences of the Proteins, DEPDC1A and DEPDC1B

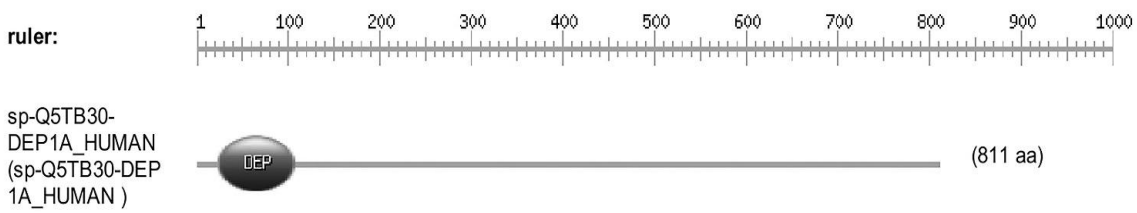
The protein sequence of the DEP domain in the two proteins- DEPDC1A and DEPDC1B, was compared using the server EMBOSS needle (http://www.ebi.ac.uk/Tools/psa/emboss_needle/) [19], a server for the pairwise sequence alignment of the respective protein sequences.

3. RESULT

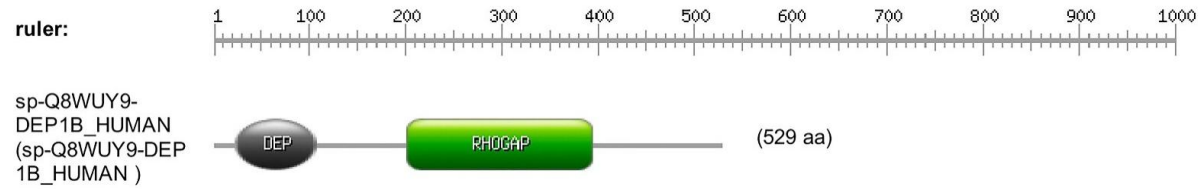
The protein sequences of DEPDC1A (UniProt ID: Q5TB30) and DEPDC1B (UniProt ID: Q8WUY9), obtained via UniProt, upon pairwise sequence alignment using EMBOSS needle showed that the two protein sequences were only 34.4% identical and 46.3% similar (Figure 1). Also, both the proteins contained DEP domain, from amino acid residue 24 to amino acid residue 108, identified using the server PROSITE (Figure 2). The sequence alignment of specifically the protein sequences of DEP domain, common in both the proteins was indicated that the two sequences are 71.8% identical, i.e. 61 amino acid residues out of 85 amino acid residues were identical, and 84.7% similar (Figure 3). Apart from the DEP domain, a second domain, RhoGAP domain, from amino acid residue 201 to amino acid residue 393 was identified using PROSITE only in DEPDC1B and but not in DEPDC1A (Figure 2). Pairwise sequence alignment of the protein sequences was followed by the prediction of the secondary structure of both the proteins using GOR IV. It was observed that DEPDC1A contained 35.76% of alpha helix, 14.06% of extended strand and 50.18% of random coil, whereas DEPDC1B consisted of 40.78% of alpha helix, 14.18% of extended strand and 44.05% of random coil (Figure 4).

```
#=======================================
#
# Aligned_sequences: 2
# 1: DEP1A_HUMAN
# 2: DEP1B_HUMAN
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 828
# Identity:     285/828 (34.4%)
# Similarity:   383/828 (46.3%)
# Gaps:         316/828 (38.2%)
# Score: 1285.0
#
#
#=======================================

DEP1A_HUMAN         1 MESQGVPPGPYRATKLWNEVTTSFRAGMPLRKHRQHFKKYGNCFTAGEAV     50
                      ||.:.|.|||||||:||||....|||.|||||||..||.|.:||||.|||
DEP1B_HUMAN         1 MEHRIVGPGPYRATRLWNETVELFRAKMPLRKHRCRFKSYEHCFTAAEAV     50

DEP1A_HUMAN        51 DWLYDLLRNNSNFGPEVTRQQTIQLLRKFLKNHVIEDIKGRWGSENVDDN    100
                      |||::|||.:.|||||||:||:|||:|||||||||||||:||.|:.:||
DEP1B_HUMAN        51 DWLHELLRCSQNFGPEVTRKQTVQLLKKFLKNHVIEDIKGKWGEEDFEDN    100

DEP1A_HUMAN       101 NQLFRFPATSPLKTLPRRYPELRKNNIE---------NFSKDKDSIFKLR    141
                      ..|:|||.:||||..|::.|. :|:.|:         ..|:::...:.:.
DEP1B_HUMAN       101 RHLYRFPPSSPLKPYPKKPPN-QKDVIKFPEWNDLPPGTSQENIPVRPVV    149

DEP1A_HUMAN       142 NLSRRTPKRHGLHLSQENGEKIKHEIINEDQENAIDNRELSQEDVEEVWR    191
                      ..|....|||.:.:.:....::.|           .|:|::.:|||:|:
DEP1B_HUMAN       150 MNSEMWYKRHSIAIGEVPACRLVH-----------RRQLTEANVEEIWK    187

DEP1A_HUMAN       192 YVILIYLQTILGVPSLEEVINPKQVIPQYIMYNMANTSKRGVVILQNKSD    241
                      .:.|.|||.|||:.|||||::.|.|..::|::|:.:.||:|||||.:||.
DEP1B_HUMAN       188 SMTLSYLQKILGLDSLEEVLDVKLVNSKFIIHNVYSVSKQGVVILDDKSK    237

DEP1A_HUMAN       242 DLPHWVLSAMKCLANWPRSNDMNNPTYVGFERDVFRTIADYFLDLPEPLL    291
                      :|||||||||||||||..:|:..|.|:|||:|||:|||||:..|.||||
DEP1B_HUMAN       238 ELPHWVLSAMKCLANWPNCSDLKQPMYLGFEKDVFKTIADYYGHLKEPLL    287

DEP1A_HUMAN       292 TFEYYELFVNILVVCGYITVSDRSSGIHKIQDDPQSSKFLHLNNLNSFKS    341
                      ||..::.||::
DEP1B_HUMAN       288 TFHLFDAFVSV-------------------------------------    298

DEP1A_HUMAN       342 TECLLLSLLHREKNKEESDSTERLQISNPGFQERCAKKMQLVNLRNRRVS    391
                            |.||.:||
DEP1B_HUMAN       299 -----LGLLQKEK-----------------------------------    306

DEP1A_HUMAN       392 ANDIMGGSCHNLIGLSNMHDLSSNSKPRCCSLEGIVDVPGNSSKEASSVF    441

DEP1B_HUMAN       307 -------------------------------------------------    306

DEP1A_HUMAN       442 HQSFPNIEGQNNKLFLESKPKQEFLLNLHSEENIQKPFSAGFKRTSTLTV    491

DEP1B_HUMAN       307 -------------------------------------------------    306

DEP1A_HUMAN       492 QDQEELCNGKCKSKQLCRSQSLLLRSSTRRNSYINTPVAEIIMKPNVGQG    541

DEP1B_HUMAN       307 -------------------------------------------------    306

DEP1A_HUMAN       542 STSVQTAMESELGESSATINKRLCKSTIELSENSLLPASSMLTGTQSLLQ    591

DEP1B_HUMAN       307 -------------------------------------------------    306

DEP1A_HUMAN       592 PHLERVAIDALQLCCLLLPPPNRRKLQLLMRMISRMSQNVDMPKLHDAMG    641
                            ||::|.|:|||||||.||||||||||::|:..|.:||.|.|..|
DEP1B_HUMAN       307 -----VAVEAFQICCLLLPPENRRKLQLLMRMMARICLNKEMPPLCDGFG    351

DEP1A_HUMAN       642 TRSLMIHTFSRCVLCCAEEVDLDELLAGRLVSFLMDHHQEILQVPSYLQT    691
                      ||:||:.|||||:||..:|||||||||.|||:||||::|||||:||..|||
DEP1B_HUMAN       352 TRTLMVQTFSRCILCSKDEVDLDELLAARLVTFLMDNYQEILKVPLALQT    401

DEP1A_HUMAN       692 AVEKHLDYLKKGHIENPGDGLFAPLPTYSYCKQISAQEFDEQKVSTSQAA    741
                      ::|:.:.:|::..|:.||..:...|...|:|:|||.:||:.|:|:...||..
DEP1B_HUMAN       402 SIEERVAHLRRVQIKYPGADMDITLSAPSFCRQISPEEFEYQRSYGSQEP    451

DEP1A_HUMAN       742 IAELLENIIKNRSLPLKEKRKKLKQFQKEYPLIYQKRFPTTESEAALFGD    791
                      :|.|||.:|.:..|..|||:||||||||.||.:|||:|||||.||.|.||.:
DEP1B_HUMAN       452 LAALLEEVITDAKLSNKEKKKKLKQFQKSYPEVYQERFPTPESAALLFPE    501

DEP1A_HUMAN       792 KPTIKQPMLI--LRKP-----KFRSLR-    811
                      ||..|..:|  |:||     :.||.|
DEP1B_HUMAN       502 KPKPKPQLLMWALKKPFQPFQRTRSFRM    529
```

Figure1. *Pairwise Sequence Alignment of the protein sequences of DEPDC1A and DEPDC1B using EMBOSS needle [19]*



a)



b)

Figure2. *Identification of the presence of the domain(s) in the proteins a) DEPDC1A and b) DEPDC1B using the server, PROSITE [21]*

```
#=======================================
#
# Aligned_sequences: 2
# 1: DEP1A_HUMAN
# 2: DEP1B_HUMAN
# Matrix: EBLOSUM62
# Gap_penalty: 10.0
# Extend_penalty: 0.5
#
# Length: 85
# Identity:      61/85 (71.8%)
# Similarity:    72/85 (84.7%)
# Gaps:           0/85 ( 0.0%)
# Score: 342.0
#
#
#=======================================

DEP1A_HUMAN        1 FRAGMPLRKHRQHFKKYGNCFTAGEAVDWLYDLLRNNSNFGPEVTRQQTI     50
                     |||.|||||||..||.|.:||||.||||||::|||.:.|||||||:||:
DEP1B_HUMAN        1 FRAKMPLRKHRCRFKSYEHCFTAAEAVDWLHELLRCSQNFGPEVTRKQTV     50

DEP1A_HUMAN       51 QLLRKFLKNHVIEDIKGRWGSENVDDNNQLFRFPA     85
                     |||:|||||||||||||:||.|:.:||..|:|||.
DEP1B_HUMAN       51 QLLKKFLKNHVIEDIKGKWGEEDFEDNRHLYRFPP     85
```

Figure3. *Pairwise Sequence Alignment of the DEP domain specific protein sequences in DEPDC1A and DEPDC1B, respectively using EMBOSS needle [19].*

```
        10        20        30        40        50        60        70
         |         |         |         |         |         |         |
MESQGVPPGPYRATKLWNEVTTSFRAGMPLRKHRQHFKKYGNCFTAGEAVDWLYDLLRNNSNFGPEVTRQ
ccccccccccccceecccceeeeecccchhhhhhhhhcecccceeecccchhhhhhhhcccccccccchh
QTIQLLRKFLKNHVIEDIKGRWGSENVDDNNQLFRFPATSPLKTLPRRYPELRKNNIENFSKDKDSIFKL
hhhhhhhhhhhcceeeeeeccccccccccccceeecccccccccccccchhhhhcccccccccchhhhh
RNLSRRTPKRHGLHLSQENGEKIKHEIINEDQENAIDNRELSQEDVEEVWRYVILIYLQTILGVPSLEEV
hhhccccccceecccccchhhhhhhhhhhhhhhhhhhhchhhhhhhhhhhhhhhhcccccccccccc
INPKQVIPQYIMYNMANTSKRGVVILQNKSDDLPHWVLSAMKCLANWPRSNDMNNPTYVGFERDVFRTIA
ccccccccceeeeeeecccccccceeeeecccccccceeeeeeeeecccccccccccceecccccchhhhh
DYFLDLPEPLLTFEYYELFVNILVVCGYITVSDRSSGIHKIQDDPQSSKFLHLNNLNSFKSTECLLLSLL
hhhcccccccchhhhheeeeeeeccceeeecccccccceeecccccchhhhhccccccccchhhhhhhhh
HREKNKEESDSTERLQISNPGFQERCAKKMQLVNLRNRRVSANDIMGGSCHNLIGLSNMHDLSSNSKPRC
hhhcccccccchhhhhhcccchhhhhhhhhhccccceeeeecccccccccceeeccceeeeeeccccce
CSLEGIVDVPGNSSKEASSVFHQSFPNIEGQNNKLFLESKPKQEFLLNLHSEENIQKPFSAGFKRTSTLT
eeecceecccccccccceeecccccccccccchhhhhccccchhhhhhhhhhhhcccccccccccceee
VQDQEELCNGKCKSKQLCRSQSLLLRSSTRRNSYINTPVAEIIMKPNVGQGSTSVQTAMESELGESSATI
ecccccccccccccccccchhhhhccccccccccccceeeeeecccccccccchhhhhhhhhhchhhh
NKRLCKSTIELSENSLLPASSMLTGTQSLLQPHLERVAIDALQLCCLLLPPPNRRKLQLLMRMISRMSQN
hhhhcccceeecccccccccccccchhhhhhhhhhhhhhhhhhhhhhcccccchhhhhhhhhhhhccc
VDMPKLHDAMGTRSLMIHTFSRCVLCCAEEVDLDELLAGRLVSFLMDHHQEILQVPSYLQTAVEKHLDYL
ccccecccccceeeeeeeeeeeeeccccccchhhhhhhhhhhhhhhhhhhccchhhhhhhhhhhhhh
KKGHIENPGDGLFAPLPTYSYCKQISAQEFDEQKVSTSQAAIAELLENIIKNRSLPLKEKRKKLKQFQKE
ccccccccccccccccccccccccccccchhhhhhhhhhhhhhhhhhhhcccchhhhhhhhhhhhhhh
YPLIYQKRFPTTESEAALFGDKPTIKQPMLILRKPKFRSLR
ccccccccccchhhhhhccccccchhhhhccccccceec

Sequence length :   811

GOR4 :
   Alpha helix     (Hh) :   290 is  35.76%
   3_10 helix      (Gg) :     0 is   0.00%
   Pi helix        (Ii) :     0 is   0.00%
   Beta bridge     (Bb) :     0 is   0.00%
   Extended strand (Ee) :   114 is  14.06%
   Beta turn       (Tt) :     0 is   0.00%
   Bend region     (Ss) :     0 is   0.00%
   Random coil     (Cc) :   407 is  50.18%
   Ambiguous states (?)  :     0 is   0.00%
   Other states          :     0 is   0.00%
```

a)

```
        10        20        30        40        50        60        70
         |         |         |         |         |         |         |
MEHRIVGPGPYRATRLWNETVELFRAKMPLRKHRCRFKSYEHCFTAAEAVDWLHELLRCSQNFGPEVTRK
ccceeecccccchhhhhhhhhhhhhhhhhhhhhhhhhcccccceehhhhhhhhhhhhhcccccccchh
QTVQLLKKFLKNHVIEDIKGKWGEEDFEDNRHLYRFPPSSPLKPYPKKPPNQKDVIKFPEWNDLPPGTSQ
hhhhhhhhhhhcceeeeecccccccccccceeeecccccccccccccccccceeeeecccccccccccc
ENIPVRPVVMNSEMWYKRHSIAIGEVPACRLVHRRQLTEANVEEIWKSMTLSYLQKILGLDSLEEVLDVK
cccceeeeeeechhhhhhceeeecccccchhhhccccccccchhhhhhhhhhhhhhhcccccchhhhhhh
LVNSKFIIHNVYSVSKQGVVILDDKSKELPHWVLSAMKCLANWPNCSDLKQPMYLGFEKDVFKTIADYYG
hhccceeeeeeecccccceeeecccccccceeeeeceeeecccccccccccccccccceeeehhhhc
HLKEPLLTFHLFDAFVSVLGLLQKEKVAVEAFQICCLLLPPENRRKLQLLMRMMARICLNKEMPPLCDGF
ccccccccccccchhhhhhhhhhhhhhhhhhhhhhhhhcccccchhhhhhhhhhhhhhcccccccccc
GTRTLMVQTFSRCILCSKDEVDLDELLAARLVTFLMDNYQEILKVPLALQTSIEERVAHLRRVQIKYPGA
ccceeeeeeceeeecccccchhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhhcccccc
DMDITLSAPSFCRQISPEEFEYQRSYGSQEPLAALLEEVITDAKLSNKEKKKKLKQFQKSYPEVYQERFP
cceeeecccccccccccccchhhcccccchhhhhhhhhhhhhhhhhhhhhhhhhhhhhcccccccccc
TPESAALLFPEKPKPKPQLLMWALKKPFQPFQRTRSFRM
cchhhhhhccccccchhhhhhhhcccccccceeeeeec

Sequence length :   529

GOR4 :
   Alpha helix     (Hh) :   221 is  41.78%
   3_10  helix     (Gg) :     0 is   0.00%
   Pi helix        (Ii) :     0 is   0.00%
   Beta bridge     (Bb) :     0 is   0.00%
   Extended strand (Ee) :    75 is  14.18%
   Beta turn       (Tt) :     0 is   0.00%
   Bend region     (Ss) :     0 is   0.00%
   Random coil     (Cc) :   233 is  44.05%
   Ambiguous states (?)  :     0 is   0.00%
   Other states          :     0 is   0.00%
```

b)

Figure4. *Prediction of Secondary Structure of the protein DEPDC1A and DEPDC1B using GOR IV [20]*

4. DISCUSSION

Both DEPDC1A and DEPDC1B, have been implicated in carcinogenesis as both the proteins have been reported to be differentially expressed in tumor cells when compared to the normal cells. However, the mechanism by which both proteins exert their pathological function might differ because of the differences in their protein sequences observed, as only 34.4% of the protein sequences were found to be identical and 46.7% similar, upon performing pairwise sequence alignment using a server, EMBOSS needle (Figure 1). Therefore, this huge difference in the protein sequence not only affects the structural characteristic of the protein but also its interaction with other proteins and hence its functionality. However, both the proteins have one common feature that is, the presence of DEP domain from amino acid residue 24 to amino acid residue 108 (a total of 84 amino acid residues) (Figure 2), as observed via the server, PROSITE, indicating that the both the protein might function similarly with respect to DEP domain mediated signaling, i.e. like DEPDC1B, DEPDC1A might also interact with G-protein coupled receptors and the negatively charged membrane phospholipids, resulting in the initiation of Wnt mediated signaling pathway [12, 13]. Out of the 84 amino acid residue DEP domain, 61 amino acid residues in the DEP domain of both the proteins, DEPDC1A and DEPDC1B, were found to be identical (71.8%) and 72 amino acid residues between the two protein being similar (84.7%) (Figure 3). The major difference in the protein sequences of the two proteins was only in the case of 13 amino acid residues, for instance, 16(K→S), 31(D→E) etc. (Figure 3), which may or may not affect the functionality of the domain and requires further research. Also, the presence of second domain, RhoGAP from the amino acid residue 201 to amino acid residue 393 in the protein DEPDC1B (Figure 2) and not in its paralog, DEPDC1A, indicates that only DEPDC1B is capable of mediating Rho GTPase signaling pathway [14], in addition to DEP domain stimulated signaling. The prediction of secondary structure of the two proteins was done using GOR IV. Due to the differences in the protein sequence of the two proteins, for instance the amino acid residue sequence from 100 to 103 was 'PELR' in case of DEPDC1A and 'PNQK' in case of DEPDC1B, resulting in the replacement of alpha helix in DEPDC1A with a random coil in case of DEPDC1B. The overall percentage variation observed in different secondary structures can be seen in Figure 4.

5. CONCLUSION

The two proteins under study, DEPDC1A and DEPDC1A play an important role in tumorigenesis as per the previously conducted studies, making them a potential biomarker, a therapeutic target and a diagnostic as well as prognostic marker. The present study focused on the better understanding of the

structural and functional characteristics of the two proteins, and therefore helping in the designing an effective and specific drug based on either of the two proteins, being implicated in various types of cancers. Even though the two proteins contains DEP domain, there exists structural difference which might result in functional differences, which must be investigated further.

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