Life Science Informatics Publications
Research Journal of Life Sciences, Bioinformatics, Pharmaceutical and Chemical Sciences
Journal Home page http://www.rjlbpcs.com/
RJLBPCS
ISSN 2454-6348

Original Research Article **DOI: 10.26479/2018.0404.60**

THE ROLE OF CIRCULAR RNA IN HUMAN GLIOBLASTOMA, OLIGODENDROMA AND LEUKEMIA

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ABSTRACT: Circular RNAs are a class of recently identified long non-coding RNAs which are covalently closed molecules and resistant to attack by exonucleases. These RNA molecules are linked to various diseases in humans including cancer. Interestingly, though they belong to the class of non-coding RNAs, many of them are known to code for protein products. The correlation between circular RNA and various forms of cancer has not been done previously. The present work tries to correlate different circular RNA and its role in human malignancies like oligodendroma, glioblastoma and leukemia.

KEYWORDS: Circular RNA; Oligodendroma; Glioblastoma; Leukemia.

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1.INTRODUCTION

Circular RNAs (circRNAs) are a class of noncoding RNA [1], first discovered in 1976, produced by back-splicing events within genes. The circRNAs formed by splicing in a linear fashion followed by their circularization by the 3′ acceptor splice site of an upstream exon. The specific characteristic structure of this class of RNA molecules protects them from exonucleaseRNase R [2]. Thus, this class of RNA molecules can exist stably inside the eukaryotic cells [3] and shared across eukaryotic tree of life [4], the expression of which is cell/tissue and developmental stage specific [5]. The circRNAs were found to consist of exons from RNA transcripts in human cells [6]. With the advent of modern high-throughput sequencing analyses and the tremendous growth in computational techniques characteristics of circRNAs are gradually deciphered, with the discovery of an increasing number of circRNAs, the number of which has recently found to be over 30,000 [7].The diversity

of circRNA in biological system is ample, as well as their functions in different cellular processes which is well evident in literature [8]. The important roles played by circRNAs in the normal biology of cell correlated with the deviation of expression patterns of circRNAs along with their characteristics (universality, conservatism, tissue/cell specificity, and stability) make them ideal candidates as biomarkers of different disease. The inherent stability of circRNAs conferred by their circular structure and exonuclease resistance, and their abundance in human blood, saliva, and gastric fluid indicates the potentialities of circRNAs as disease biomarkers. An increasing number of studies also reported that circRNAs play important roles in the development and progression of diseases including cancer [9]. In particular, circRNAs have shown great potential in cancer diagnosis, prognosis, and therapy, thus the present work emphasizes to reveal this exciting class of transcripts in regulating gene expression and discuss their role in cancer. Throughout the past decade, nearly 90,000 different circRNAs were identified in humans [10]. Majority of these circRNAs are derived mainly from annotated exons and the remaining is found to be derived from un-translated regions (UTRs), introns and un-annotated regions of the genome. It has been reported that the circRNAs are most commonly derived from two to three exons and their lengths would vary between a hundred and four thousand nucleotides [10]. It is interesting to note that though the circRNAs in humans are considered to belong to the class of non-coding RNAs, some of these circRNAs in humans have protein coding potentials [11]. The existences of circular RNAs have long been known; however, their actual functionalities till date are merely speculative. The reports on the structural and functional aspects of circRNAs are scarce in literature particularly in relation to cancer in humans. In this work, an attempt has been made to decipher the structural details of the protein coding potentials of the circRNAs in humans. For that purpose, the amino acid sequences of the proteins from the circRNAs in humans having experimental validations of protein coding were collected from the circRNADb (http://202.195.183.4:8000/circrnadb/circRNADb.php). The amino acid sequences were analyzed and the involvements of the proteins in the development of only different forms of human cancers were considered. The previously unappreciated role of circRNAs have been documented to act in species-specific manner across species and have the potential to present genetic information in new orientations which is unique compared to their parent transcript. This proves the unique role of circRNA in evolutionary dynamics [12]. The main focus of the current research on the circRNAs is directed towards the identifications of their mode of biogenesis and their subsequent involvements in disease onset. This study may pave the pathway to future structural biological works to elucidate the bio-molecular details of these special proteins.

2. MATERIALS AND METHODS

2.1. Collection of data

The information on the circRNAs in humans has been accessed from circRNADb database, which can be browsed selecting the Protein Expression Evidence keyword, which revealed 72 circRNA. The amino acid sequences of the proteins encoded by the circRNAs, which are responsible for some form of cancer has been selected for the study. The proteins were sub-divided into mostly three categories, glioblastoma, oligodendroma and leukemia. The glioblastoma contained 14 entries, oligodendroma contained 13 entries and leukemia contained 6 entries.

2.2. Sequence analyses of the proteins

The amino acid sequences retrieved from the 72 cancer causing circRNAs were investigated to detect the presence of specific domains in the proteins. The Pfam algorithm was used for the purpose [13].

3. RESULTS AND DISCUSSION

The protein from hsa_circ_00341 was identified from human chromosome chr4: 72313362-72352735. The protein is involved in oligodendroma in humans. The sequence analyses of the protein revealed the presence of bicarbonate transporter family domain, the deregulation of which may have both diagnostic and therapeutic potential in cancer treatment [14]. The protein from hsa_circ_01271 was identified from human chromosome chr3: 48451704-48457168. The protein is involved in glioblastoma in humans. The sequence analyses of the protein revealed the presence of Plexin cyplasmic Ras GAP family domain. The Plexins, comprising Plexin-A, -B, -C, and -D subfamilies, are receptors for semaphorins governing cell adhesion and migration, thus have played important role in tumorigenesis and cancer [15]. The protein from hsa_circ_02276 was identified from human chromosome chr9: 131369882-131375764.The protein is involved in oligodendroma in humans. The sequence analyses of the protein revealed the presence of Spectrin family domain. Mutations of spectrin lead to various human diseases including cancer [16]. The protein from hsa_circ_02306 and hsa_circ_02838 were identified from human chromosome chr18: 32407556-32444026 and chr7: 158531713-158540971 respectively. Both of the proteins were found to be involved in the generation of glioblastoma in humans. The protein from hsa_circ_04264 was identified from human chromosome chr5: 150095126-150121719.The protein is involved in oligodendroma in humans. The sequence analyses of the protein revealed the presence of Dynactin p62 family domain. The protein from hsa_circ_06318 was identified from human chromosome chr13: 113170753-113181798. The protein is involved in glioblastoma, oligodendroma in humans. The sequence analyses of the protein revealed the presence of Spc97/Spc98 family domain. While the protein from hsa_circ_06619 was identified from human chromosome chr14: 77930940-77932010. The protein is involved in leukemia in humans. Whereas, the protein from hsa_circ_08893 was identified from human chromosome chr2: 201852984-201862263, which is

involved in leukemia in humans. The sequence analyses of the protein revealed the presence of Hyccin family domain, which affects human myelination status [17].The protein from hsa_circ_12092 was identified from human chromosome chr1: 51121113-51204626. The protein is involved in glioblastoma in humans. While, the protein from hsa_circ_12152 was identified from human chromosome chr9: 87482157-87570432. The protein is involved in glioblastoma in humans. The sequence analyses of the protein revealed the presence of Protein Tyrosine Kinase family domain. The protein tyrosine kinases are a family of signaling molecules involved in different cancers and can be considered as the modern target for anticancer treatment [18]. The protein from hsa_circ_13000 was identified from human chromosome chr10: 11971863-11994248. The protein is involved in oligodendroma in humans. The sequence analyses of the protein revealed the presence of Upf-2 family domain. Whereas, the protein from hsa_circ_16580 was identified from human chromosome chr11: 50244119-50246949.The protein is involved in glioblastoma in humans. The sequence analyses of the protein revealed the presence of Septin family domain. Septins are GTP-binding proteins, evolutionarily and structurally related to the *Ras* oncogene. Alterations in Septin expression levels have been previously reported in progression of different cancers [19]. The protein from hsa_circ_17819 was identified from human chromosomechr3: 47098310-47103836. The protein is involved in glioblastoma, oligodendroma in humans. The protein from hsa_circ_20275 was identified from human chromosome chr15: 44053621-44055404. The protein is involved in glioblastoma in humans. The protein from hsa_circ_20832 was identified from human chromosome chr4: 114232410-114267178. The protein is involved in glioblastoma, oligodendroma in humans. The sequence analyses of the protein revealed the presence of Zu 5 family domain. The protein from hsa_circ_20838 was identified from human chromosome chr1: 118454615-118461358. The protein is involved in glioblastoma, oligodendroma in humans. The sequence analyses of the protein revealed the presence of Macrofamily domain. Macrodomains are evolutionarily conserved structural domains found involved in different cellular physiological processes. Human Macrodomain overexpression has been previously linked to cancer progression in humans [20]. The protein from hsa_circ_21354 was identified from human chromosome chr8: 42259305-42260979. The protein is involved in glioblastoma, oligodendroma in humans. The sequence analyses of the protein revealed the presence of Eukaryotic Porin 3 family domain. The protein from hsa_circ_21471 was identified from human chromosomechr1: 151204146-151205179. The protein is involved in oligodendroma in humans. The protein from hsa_circ_22823 was identified from human chromosome chr2: 183817132-183818059. The protein is involved in glioblastoma, oligodendroma in humans. The sequence analyses of the protein revealed the presence of Nckap 1 family domain. Whereas, the protein from hsa_circ_23018 was identified from human chromosome chr2: 183799479-183818059. The protein is involved in oligodendroma in humans. The sequence analyses of the protein revealed the presence of Nckap 1 family domain. The high expression of

NCKAP is reported to be associated with progression of human cancer [21]. The protein from hsa_circ_23253 was identified from human chromosome chr3: 47079155-47103836. The protein is involved in glioblastoma in humans. The sequence analyses of the protein revealed the presence of WW family domain. The WW family proteins have been reported to be responsible for different human cancer progression [22]. The protein from hsa_circ_25375 was identified from human chromosome chr11: 972061-1000598. The protein is involved in oligodendroma in humans. The sequence analyses of the protein revealed the presence of Adaptin N family domain. While, the protein from hsa_circ_26646 and hsa_circ_2927 was identified from human chromosome chr10: 79769294-79784900 and chr10: 79781617-79784900 respectively and are responsible for leukemia in humans. The sequence analyses of the protein revealed the presence of RNA pol Rpb 1 family domain. The protein from hsa_circ_27515 was identified from human chromosome chr10: 121685547-121689943. The protein is involved in leukemia in humans. The sequence analyses of the protein revealed the presence of DDHD family domain. The protein from hsa_circ_28880 was identified from human chromosome chr20: 21319681-21324846. The protein is involved in glioblastoma, oligodendroma, leukemia in humans.

4. CONCLUSION

Earlier works have reported correlation between circRNA and different cancer [23][24][25][26]. The present work correlates different circular RNA and its role in human malignancies like oligodendroma, glioblastoma and leukemia along with the structural properties of the proteins encoded by the circRNA. The proteins encoded by different circRNA have been observed to be associated with different human cancer. The different protein domains could be further studied for their probable evolutionary origin and could also be explored for therapeutic management of the diseases.

CONFLICT OF INTEREST

None.

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