Computational study on protein interactions of CDKN2C and its impact on cancer studies.

Abstract:

CDKN2C is a tumour suppressor that suppress bone cancers like osteosarcoma and multiple myeloma by regulating cell cycle. Deletions or mutations in the gene can leads to tumour progression and worst survival however over expression leads to radiation sensitivity, G1 phase arrest and trigger apoptosis in osteosarcoma. Study on CDKN2C protein and its role in bone cancer is right now gaining evidence and few of the proteins like CDKN1C, CDKN2D, CCNL2 show primary level interactions and gene CDK4 is found be co expressed with CCND1 through prediction analysis and observed co-expression of homologs in other species through STRING database tool.

Key words:CDKN2C protein;CCND1;Osteosarcoma;Multiple myeloma;G1 phase arrest;co-expression

Introduction:

Limited radiosensitivity to osteosarcoma is one of the major posing challenge and studies of Qiujian Lian etal 2024 the protein CDKN2C increases radiosensitivity by causing G1 phase cell cycle arrestand subsequent apoptosis. G1 phase arrest is mediated by deregulates the expression of phosphorylated RB protein.

Deletions at chromosome 1 is identified in 7 to 4% of the multiple myeloma cancers and CDKN2C presence at 1p32.3 has been identified as one of the potential targets for deletion in multiple myeloma patients (Qiujian Lian etal 2024). One of the examples is homozygous deletion of the gene (Cox C et al.,2005). Using high resolution mapping the deletion of the gene is identified in about 40% of the multiple myeloma cell lines (Kulkarni MS et al., 2002, Dib A et al., 2006).

CDKN2C deviation in expression is known to be recorded with so many cancers but for the first time reports on its upregulation in expression in SCLC at both gene and protein level is done by Guo-Sheng Li et al.,2022 and CDKN2C expression is related to immune microenvironment and it can serve as one of the important prognostic marker in immune therapy. Immune checkpoint inhibitor related treatment is one of the promising treatments for SCLC but however its benefits is limited to few of the patient's due to lack of availability in biomarkers(Esposito G et al 2020).

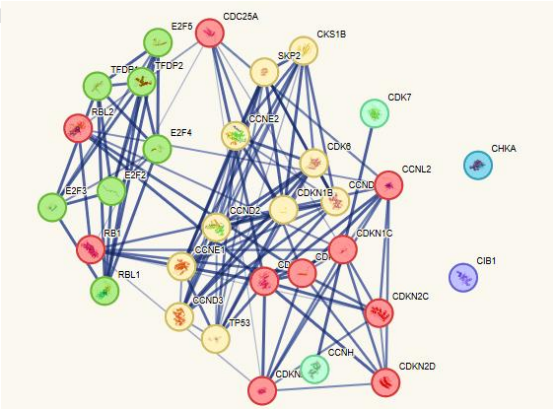

Figure:1: Study of Protein interactions of CDKN2C using STRING database by applying clusters with count of 6 using k means algorithm. Settings are customised to confidence medium score of 0.400.

CDKN1C, CDKN2D, CCNL2 are the few among the proteins that show primary level of interactors with CDKN2C and whereas CDKN1C, E2F4 are the second level of interactors of protein CDKN2C through proteins CCNL2.

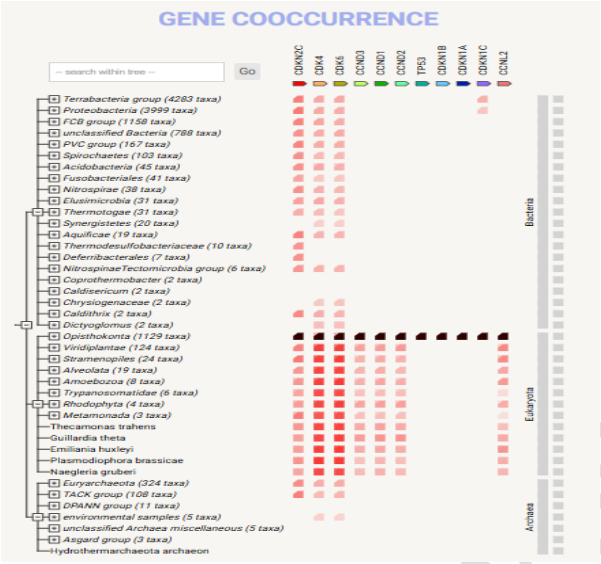

Figure:2 Study of Gene Co-occurrence ofprotein CDKN2C among different taxa

Gene occurrence has marked with CDK4 and CDK6 in Eukaryota and whereas low occurrence is seen with Archaea.

k means clustering algorithm and working principle:

k means clustering algorithm is an unpredicted machine learning methodology that clusters data based on predefined number (K) of distinct non overlapping groups with feature similarity. The goal of the algorithm is to minimise the variation and to group the defined points with total similarity in to one group and also to be distinct entirely when marked with another group in a cluster. The algorithm assigns data using Euclidean distance of the data points to the nearest centroid and recalculates the mean of the assigned points to the centroid and the process repeats with initial randomly chosen centroids until the assigned cluster stabilise and indicates convergence as same group.

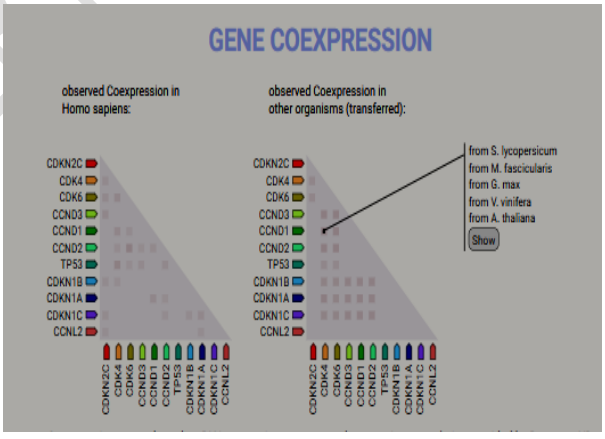

Figure: 3 Gene Co-expression studies of CDKN2C protein in homo sapiens and other related organisms. Based on Predicted association, CDK4 and CCND1, observed co-expression of homologs in other species through STRING database tool.

Study of transcripts for the gene RANKL using AUGUSTUS tool using FASTA sequence collected from NCBI database:

AUGUSTUS is a popular open-source software tool used for eukaryotic gene prediction, and utilizes a Generalized Hidden Markov Model (GHMM) to predict gene structures based on sequence alone or incorporates evidence from RNA-SeqESTs, and protein alignments through performing *ab initio* prediction. It is available both as via web interface (WebAUGUSTUS) or local installation through Git hub.

RANKL: Comparison of RANKL transcripts and protein sequence between Homo sapiens (GenBank: AF019047.1) andmus musculus {(GenBank: AF019048.1) curated from NCBI database using mRNA sequence as the genome input}selecting options both strands and only complete genes with alternative transcripts as few instead of many or none.

Homo sapiens:

ATGCGCCGCGCCAGCAGAGACTACACCAAGTACCTGCGTGGCTCGGAGGAGATGGGCGG
CGGCCCCGGAGCCCCGCACGAGGGCCCCCTGCACGCCCCGCCGCCGCCTGCGCCGCACC
AGCCCCCCGCCGCCTCCCGCTCCATGTTCGTGGCCCTCCTGGGGCTGGGGCTGGGCCAGG
TTGTCTGCAGCGTCGCCCTGTTCTTCTATTTCAGAGCGCAGATGGATCCTAATAGAATATCA
GAAGATGGCACTCACTGCATTTATAGAATTTTGAGACTCCATGAAAATGCAGATTTTCAAG
ACACAACTCTGGAGAGTCAAGATACAAAATTAATACCTGATTCATGTAGGAGAATTAAACA
GGCCTTTCAAGGAGCTGTGCAAAAGGAATTACAACATATCGTTGGATCACAGCACATCAG
AGCAGAGAAAGCGATGGTGGATGGCTCATGGTTAGATCTGGCCAAGAGGAGCAAGCTTG
AAGCTCAGCCTTTTGCTCATCTCACTATTAATGCCACCGACATCCCATCTGGTTCCCATAAA
GTGAGTCTGTCCTCTTGGTACCATGATCGGGGTTGGGCCAAGATCTCCAACATGACTTTTA
GCAATGGAAAACTAATAGTTAATCAGGATGGCTTTTATTACCTGTATGCCAACATTTGCTTT
CGACATCATGAAACTTCAGGAGACCTAGCTACAGAGTATCTTCAACTAATGGTGTACGTCA
CTAAAACCAGCATCAAAATCCCAAGTTCTCATACCCTGATGAAAGGAGGAAGCACCAAGT
ATTGGTCAGGGAATTCTGAATTCCATTTTTATTCCATAAACGTTGGTGGATTTTTTAAGTTAC
GGTCTGGAGAGGAAATCAGCATCGAGGTCTCCAACCCCTCCTTACTGGATCCGGATCAGG
ATGCAACATACTTTGGGGCTTTTAAAGTTCGAGATATAGATTGA

mus musculus:

ATGCGCCGGGCCAGCCGAGACTACGGCAAGTACCTGCGCAGCTCGGAGGAGATGGGCAG
CGGCCCCGGCGTCCCACACGAGGGTCCGCTGCACCCCGCGCCTTCTGCACCGGCTCCGGC
GCCGCCACCCGCCGCCTCCCGCTCCATGTTCCTGGCCCTCCTGGGGCTGGGACTGGGCCA
GGTGGTCTGCAGCATCGCTCTGTTCCTGTACTTTCGAGCGCAGATGGATCCTAACAGAATA
TCAGAAGACAGCACTCACTGCTTTTATAGAATCCTGAGACTCCATGAAAACGCAGATTTGC
AGGACTCGACTCTGGAGAGTGAAGACACACTACCTGACTCCTGCAGGAGGATGAAACAA
GCCTTTCAGGGGGCCGTGCAGAAGGAACTGCAACACATTGTGGGGCCACAGCGCTTCTC
AGGAGCTCCAGCTATGATGGAAGGCTCATGGTTGGATGTGGCCCAGCGAGGCAAGCCTGA
GGCCCAGCCATTTGCACACCTCACCATCAATGCTGCCAGCATCCCATCGGGTTCCCATAAA
GTCACTCTGTCCTCTTGGTACCACGATCGAGGCTGGGCCAAGATCTCTAACATGACGTTAA
GCAACGGAAAACTAAGGGTTAACCAAGATGGCTTCTATTACCTGTACGCCAACATTTGCTT
TCGGCATCATGAAACATCGGGAAGCGTACCTACAGACTATCTTCAGCTGATGGTGTATGTC
GTTAAAACCAGCATCAAAATCCCAAGTTCTCATAACCTGATGAAAGGAGGGAGCACGAAA
AACTGGTCGGGCAATTCTGAATTCCACTTTTATTCCATAAATGTTGGGGGATTTTTCAAGCT
CCGAGCTGGTGAAGAAATTAGCATTCAGGTGTCCAACCCTTCCCTGCTGGATCCGGATCA
AGATGCGACGTACTTTGGGGCTTTCAAAGTTCAGGACATAGACTGA

Amino acid sequence:

Homo sapiens:

MRRASRDYTKYLRGSEEMGGGPGAPHEGPLHAPPPPAPHQPPAASRSMFVALLGLGLGQVV
CSVALFFYFRAQMDPNRISEDGTHCIYRILRLHENADFQDTTLESQDTKLIPDSCRRIKQAFQG
AVQKELQHIVGSQHIRAEKAMVDGSWLDLAKRSKLEAQPFAHLTINATDIPSGSHKVSLSSWY
HDRGWAKISNMTFSNGKLIVNQDGFYYLYANICFRHHETSGDLATEYLQLMVYVTKTSIKIPS
SHTLMKGGSTKYWSGNSEFHFYSINVGGFFKLRSGEEISIEVSNPSLLDPDQDATYFGAFKVR
DID

Mus Musculus:

MRRASRDYGKYLRSSEEMGSGPGVPHEGPLHPAPSAPAPAPPPAASRSMFLALLGLGLGQVV
CSIALFLYFRAQMDPNRISEDSTHCFYRILRLHENADLQDSTLESEDTLPDSCRRMKQAFQGA
VQKELQHIVGPQRFSGAPAMMEGSWLDVAQRGKPEAQPFAHLTINAASIPSGSHKVTLSSWY
HDRGWAKISNMTLSNGKLRVNQDGFYYLYANICFRHHETSGSVPTDYLQLMVYVVKTSIKIP
SSHNLMKGGSTKNWSGNSEFHFYSINVGGFFKLRAGEEISIQVSNPSLLDPDQDATYFGAFKV
QDID

Study of Transcripts in protein Matrilin 3 in Homo sapiens present on chromosome 2 using AUGUSTUS online tool :NCBI Reference Sequence: NG_008087.1:

Nucleotide Transcripts:

GTGTTTGCAAGAGCAGACCCTTGGACCTGGTGTTTATCATTGATAGTTCTCGTAGCGTACG
GCCCCTGGAATTCACCAAAGTGAAAACTTTTGTCTCCCGGATAATCGACACTCTGGACATT
GGGCCAGCCGACACGCGGGTGGCAGTGGTGAACTATGCTAGCACTGTGAAGATCGAGTTC
CAACTCCAGGCCTACACAGATAAGCAGTCCCTGAAGCAGGCCGTGGGTCGAATCACACCC
TTGTCAACAGGCACCATGTCAGGCCTAGCCATCCAGACAGCAATGGACGAAGCCTTCACA
GTGGAGGCAGGGGCTCGAGAGCCCTCTTCTAACATCCCTAAGGTGGCCATCATTGTTACA
GATGGGAGGCCCCAGGACCAGGTGAATGAGGTGGCGGCTCGGGCCCAAGCATCTGGTATT
GAGCTCTATGCTGTGGGCGTGGACCGGGCAGACATGGCGTCCCTCAAGATGATGGCCAGT
GAGCCCCTAGAGGAGCATGTTTTCTACGTGGAGACCTATGGGGTCATTGAGAAACTTTCCT
CTAGATTCCAGGAAACCTTCTGTGCGCTGGACCCCTGTGTGCTTGGAACACACCAGTGCC
AGCACGTCTGCATCAGTGATGGGGAAGGCAAGCACCACTGTGAGTGTAGCCAAGGATACA
CCTTGAATGCCGACAAGAAAACGTGTTCAGGTGAGGCCTGTGTAGGGGGCCGTGACTGA

Protein sequence:

VCKSRPLDLVFIIDSSRSVRPLEFTKVKTFVSRIIDTLDIGPADTRVAVVNYASTVKIEFQLQAYT
DKQSLKQAVGRITPLSTGTMSGLAIQTAMDEAFTVEAGAREPSSNIPKVAIIVTDGRPQDQVNE
VAARAQASGIELYAVGVDRADMASLKMMASEPLEEHVFYVETYGVIEKLSSRFQETFCALDP
CVLGTHQCQHVCISDGEGKHHCECSQGYTLNADKKTCSGEACVGGRD

Conclusion:

By this study we can conclude study of CDKN2C protein interactions and coexpression analysis can help in prediction of biomarkers like CDK4, CCND1 for targeting the cell cycle progression in cells with deletions of CDKN2C gene.

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