SIDE EFFECT SIMILARITY OF A0A022RDQ0 PROTEIN AND CYCLOOXYGENASES DURING DRUG TARGETING IN CANCER TREATMENT

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ABSTRACT

This work predicts the side effect similarity of A0A022RDQ0 protein to Prostaglandin G/H synthase 1 and 2 (PG/Hs1 and PG/Hs2), also referred to as COX 1 and COX 2 respectively, during drug targeting in cancer treatment. Identification of proteins responsible for colorectal cancer as a model case in this study was done from Uniprot database. Sequence alignment of identified proteins to A0A022RDQ0 as an insight to side effect similarity was carried out using Clustal Omega bio informatic tool. Results reveal that PG/Hs1 and PG/Hs2 are major causes of colorectal cancer. Sequence alignment of PG/Hs1 and PG/Hs2 to A0A022RDQ0 show 21.43% and 21.03% similarity respectively thus only a slight fraction of side effects should be caused by drugs during cancer remediation.

KEYWORDS: Side Effect, A0A022RDQ0 Protein, Prostaglandin G/H synthase, Drug Targeting

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INTRODUCTION

A0A022RDQ0 protein is made up of 339 amino-acid sequences (fig 1) and has a WD40 domain (Finn *et al.*, 2016). This domain is associated with several functions including apoptosis, transcription and cytoskeleton assembly. WD40 is thought to significantly function in multi-protein assembly involving tandem repeats that serve as firm scaffold during protein interaction (Finn *et al.*, 2016; Hellsten *et al.*, 2013; Marchler-Bauer *et al.*, 2015, 2011, 2009, 2004). WD40 domain comprises of 11-24 dipeptide residues referred as GH and the other with 40 residues located at C terminus is responsible for the name WD40. Tryptophan-aspartic acid is usually the 40th residue and is a preserved core located between GH and WD. This makes possible steady and reciprocal binding of the protein. A0A022RDQ0 as a model protein in this study is chosen because it contains a WD40 domain which performs several critical functions stated earlier and is present in several eukaryotic proteins (Anakaa *et al.*, 2017).

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MQVESALSVVGPKPTLSTVTHGFAPPGANAKQRTSSLEAPIMLLSGHQSAVYTMKFNPA
GTVIASGSHDRDIFLWNVNSDCKNFMVLRGHKNAVLDLQWNTDGSQIISTSPDKTLRAW
DVETGKQIKKMIGHLFVNSCCPARRGPPLIVSGSDDGTAKLWDMRQRGSIQSFPDKYQI
TAVGFSDASDKIYTGIDNDVKVWDLRRTEPVMKLQGHHDMITGMQLSPDGSYLLTNS
MDCTLRIWDMRPYAPQNRCKILEGHQHNFEKNLLRCSWSPDGSKVTAGSSDCMVYVW
DTTSRRILYKLPGHTGSVNECVFHPNENIIGSCSSDKQIYLGEI
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Figure 1: Amino acid sequence of A0A022RDQ0 protein.

Prostaglandin G/H synthase proteins (PG/Hs) also referred to as COX include PG/Hs1 (COX 1) and PG/Hs2 (COX

2) are homo sapiens based precursor enzymes that mainly function in the biosynthesis of prostaglandin (Mbonye et al., 2006). Although a high level of functional and structural similarity is possessed by these isoforms, COX 1 is widely expressed in non-mobile cells as with COX 2 that is stimulated by different tissues from fibroblast to polished cells of the muscles in acknowledgement of growth determinants such as cytokines. Expression of COX 2 beyond limit is a major cause of colorectal cancer, hence clearly indicating that overexpression of prostaglandin is significantly associated with tumours. Among other tumours, colorectal cancer has been recorded the forth mortal type and third widely distributed in the universe (Gandomani *et al.*, 2017; Hagggar et al., 2008). Colorectal cancer as a model in this study is adopted because of its close resemblance to other human tumours.

Several administered drugs have many off-targets from their primary target thus, causing numerous physiological responses because of perturbed signalling and metabolic pathways thus, creating side effects (Zhao *et al.*, 2010). Traditionally, high sequence similarity between target and off-target proteins indicates less side effects after drug administration and vice-versa (Brouwers *et al.*, 2011) thus, the need to explore the percentage of similarity between A0A022RDQ0 and some cancer-causing proteins that include cyclooxygenases. The side effect similarity between these proteins is further necessary to create an improved understanding of drug action and adverse effects between several proteins during drug targeting. This work predicts the side effect similarity of A0A022RDQ0 protein and human cyclooxygenases during drug targeting in cancer treatment. Exploring the proteins responsible for colorectal cancer as a model case and sequence alignment for similarity of these proteins to that of A0A022RDQ0 will also be checked.

MATERIALS AND METHODS

Uniprot database was used to explore proteins responsible for colorectal cancer. Multiple sequence alignments of A0A022RDQ0 to cancer causing proteins were done using clustal omega database.

RESULT

Table 1 shows the names, Uniprot entry number (EN), gene names and length of amino acid sequence (AAS) of identified proteins responsible for colorectal cancer. See fig 2 and 3 for amino acid sequences. Fig 2 and 3 shows the amino acid sequence of COX 1 and COX 2 respectively.

Table 1: Proteins responsible for colorectal cancer

Protein name	Organism	Uniprot EN	Gene names	Length of AAS
Prostaglandin G/H synthase 1(COX 1)	Human	P23219	PTGS1 COX1	559
Prostaglandin G/H synthase 2(COX 2)	Human	P35354	PTGS2 COX2	604

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MSRSLLLWFLFLLLLPLPVLLADPGAPTFVNPCCYYPCQHQGICVRFGLDRYQCDCTRGTG
YSGPNCTIPGLWTWLRNSLRSPSFTHFLLTHGRWFWFVNATFIREMLMRLVLTVRSNLIP
SPPTYNSAHDYISWESFSNVSYTRILPSVPKDCPTPMGTGKGKKQLPDAQLLARRFLLRRKFI
PDPQGTNLMFAFFAQHFTHQFFKTSGKMGPFGTKALGHGVLDLGHYGDNLERQYQLRLFK
DGKLKYQVLDGEMYPPSVEEAPVLMHYPRGIPPQSQMAVGQEVFGLLPGLMLYATLWLRE
HNRVCDLLKAEHPTWGDEQLFQTTRLILIGETIKIVIEEYVQQLSGYFLQLKFDPELLFGVQF
QYRNRIAMEFNHLYHWHPLMPDSFKVGSQEYSYEQFLNTSMLVDYGVEALVDAFSRQIA
GRIGGGRNMDHHILHVAVDVIREMRLQPFNEYRKRFGMKPYTSFQELVGEKEMAAELE
ELYGDIDALEFYPGLLLEKCHPNSIFGESMIEIGAPFSLKGLLGNPICSPEYWKPSTFGGEVGF
NIVKTATLKKLVCLNTKTCPVVSFRVPDASQDDGPAVERPSTEL
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Figure 2: Amino acid sequence of COX 1.

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MLARALLLCAVLALSHTANPCCSHPCQNRGVCMSVGFQYKCDCTRGTGFYGENCSTPEFLT
RIKLFLKPTPNTVHYILTHFKGFWNVNNIPFLRNAIMSYVLTSRSHLIDSPPTYNADYGYKS
WEAFSNLSYYTRALPPVPDDCPTPLGVKGKKQLPDSNEIVEKLLLRRKFIPDPQGSNMMFAF
FAQHFTTHQFFKTDHKGPAFTNGLGHGVLDLNHIYGETLARQRLRLFKDGKMKYQIIDGE
MYPPTVKDTQAEMIYPPQVPEHLRFAVGQEVFGLVPGLMMYATIWLREHNRVCDVLKQEH
PEWGDEQLFQTSRLILIGETIKIVIEDYVQHLSGYHFKLKFDPELLFNKQFQYQNRIAAEFNTL
YHWHPLLPDTFQIHDQKYNYYQFIYNNISILLEHGITQFVESFTRQIAGRVAGGRNVPPAVQK
VSQASIDQSRQMKYQSFNEYRKRFMLKPYESFEELTGEKEMSAELEALYGDIDAVELYPAL
LVEKPRPDAIFGETMVEVGAPFSLKGLMGNVICSPAYWKPSTFGGEVGFQIINTASIQSLICN
NVKGCPFTSFSVPDPELIKTVTINASSRSGLDDINPTVLLKERSTEL
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Figure 3: Amino acid sequence of COX 2.

Fig 4 and 5 reports 21.43% and 21.03% similarity in sequence between A0A022RDQ0 to COX1 and COX 2.

A0A022RDQ0	-----MQVESALSVVCPKP-----TELSTVT	21
COX-1	MSRSLLLWFLFLLLPLPVLADPGAPTPVNPCCYYPQHQGICVRFGLDRYQCDCTR	60
	: : * * : *	: . .
A0A022RDQ0	HGFAPPCANAK-----QRTSSLEAP-----IMLLSGHQS-----AV-----YTMKFNPA	61
COX-1	TGYSGPNCTIPGLWTWLRNSLRPSPSFTHFLTHGRWFWEFVNATFIREMLRLVLTVR	120
	* : : * . . * * : * : * * : * . : . .	
A0A022RDQ0	TVIAS---GSHDRIFLWN-----VNSDCKNFMVLGHNNA-----	94
COX-1	NLIPSPPTYNASHDYISWESFSNVSYTRILPSVPRDCPTPMGTGKQQLPDAQLLARR	180
	. : * * . : * : * : * . * * . * : * : *	
A0A022RDQ0	-----	94
COX-1	LLRRKFI PD PQGTNLMAFAFAQHFTHQFFKTSCKMCPGFTKALGHCVDLGHYGDNLERQ	240
A0A022RDQ0	-----VL-----	96
COX-1	YQLRLFKDGKLYQVLDGEMYPSPVEEAPVLMHYPRGIPQSQMAVGQEVFGLLPGLMLY	300
	*	
A0A022RDQ0	DLQWNTDGSQIISTSPDKTLRAMDVET-----GKQIKKMIGHLFVWN-S-CCPAR	144
COX-1	ATLWLREHNRVCDL-LKAEHPTWGDQLPQTTRLILIGETIKIVIEEYVQQLSGYFLQLK	359
	* : . : . . : * * * : * * : * . . : :	
A0A022RDQ0	RGPLIVSGSD-----DGTAKLMDMRQRCISQSFDPKYQITAVGF-----	184
COX-1	FDPELLF-GVQFYRNRIAMEFNHLYHWP-----LMPDSFKVGSQEYSYEQFLFNTS	411
	* * : . * : * . : * * : * * : : : :	
A0A022RDQ0	-----SDASDKITYTGGIDNDVKVW----DLRRTBPVMKLQGHDMITGMQL	226
COX-1	MLVDYGVREALVDAFSRQIAGRICGGRNMDHHI LHVAVDVIRESEMRQL-----	460
	* * * : * : * : * : * . * : *	
A0A022RDQ0	SPDGSYLLTNSMDCITLRIDMRPYAPQNRCKILE-----CHQH--NFEKNLL--R	273
COX-1	-PFN-----EYPRKFGKPYTSFQELVGEKEMAELEELYGDIDALEFYPLGLEK	510
	* : : * : * : . . * * * . . : * * :	
A0A022RDQ0	CS-----WSPDGSKVTAGSSDCMVYVWDTS-----	299
COX-1	CHPNSIFGESMI EICAPFSLKGLLGNPICSPFYWKPSFTGCEVGFNIWKATATLKKLVCLN	570
	* : * . * * . * * . : :	
A0A022RDQ0	----RRIYLKLPCHTGSVNECVFHPNEPIIGSCSSDKIYLGEL	339
COX-1	TKTCPYVSFRVPDASQDDGPAVERPSTEL-----	599

Figure 4: Sequence similarity of 21.43% between A0A022RDQ0 to COX 1.

Figure 5: Sequence similarity of 21.03% between A0A022RDO0 to COX 2.

Results in table 1 reveal that COX 1 and COX 2 that are synthesized by Prostaglandin G/H synthase are responsible for colorectal cancer. This is in consonance with the findings of Tomozawa *et al.*, 2000 who reported that overexpression of COX 2 causes colorectal cancer. The identification of COX 1 to be associated with colorectal cancer further correlates with the findings of Hwang *et al.*, 1998 that diagnosed the expression of COX 1 in 30 of 44 tumour patients examined. In ascertaining results obtained in this study, Hwang *et al.*, 1998 concluded overexpression of COX may not necessarily be restricted to colon cancer but may be attributed to other tumours that are epithelial based. This is evident as the results obtained above report COX 1 and 2 to be key in colorectal cancer. Sahin *et al.*, 2008 also implicated COX2 as cause of several cancers

including colorectal cancer which corroborates results obtained in this study. In substantiating results in table 1, Dore, 2011; Zha *et al.*, 2004 and Golijanin *et al.*, 2004 have all associated COX enzyme with cancer of various kinds.

Fig 4 and 5 reports 21.43% and 21.03% similarity between A0A022RDQ0 with COX 1 and COX 2 respectively predicting that only a small fraction of side effects should be observed. This is in line with Brouwers *et al.*, 2011 that realised higher side effects (64%) upon targeting proteins that are close in network as with lesser effects observed (5.8%) in overlapping proteins having performed related experiment. It should be known that a subnetwork of corresponding proteins being targeted by a drug is not necessarily a determinant of adverse effect similarity, it gives molecular insights based on side effects.

CONCLUSIONS

This analysis is intended to set the basis of further studies on the side effect similarity between A0A022RDQ0 a recently characterised ribonuclear protein and some PG/Hs responsible for colorectal cancer. Although more analysis and clinical studies need to be done, this study shows that COX1 and COX2 are responsible for colorectal cancer and only a small fraction of side effects will be observed in the network of A0A022RDQ0 and COX during drug administration in cancer treatment implying the activity of A0A022RDQ0 protein will not necessarily be disturbed.

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