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Insilico Molecular Characterization of Potential Drug Targets in Oral Cancer

Vinod P. Sinoorkar[1], Vishakha U. Doke[2]
[1, 2]*PG Department of Bioinformatics, Walchand centre for biotechnology Solapur, Maharashtra, India.*

Abstract: ***Oral cancer is the most frequent type of cancer occurring in India. It has ranked in top three types of cancer in the country. Most oral cancers occur as squamous cell carcinomas (SCCs) and many OSCCs develop from premalignant conditions of the oral cavity. Development oral cancer is mostly due to tobacco, cigarette, alcohol and palatal lesion. Multiple deregulations of genes in the MYC module is the more aggressive phenotype of tumor development. CXCL1 is the reason that transform normal fibroblasts(NOFs) into senescent Cancer-associated fibroblasts(CAFs) via an autocrine mechanism. Distinct gene expression patterns between carcinomas of the floor of the mouth and oral tongue cancer can be indicated by XIAP. Hence the present work was carried out to understand the detailed molecular features underlying the functions of MYC, CXCL1 and XIAP emphasizing their key role in the onset of oral cancer using various in-silico tools. These preliminary investigations can contribute to uncover the specific molecular functions of these drug targets and pave a new dimension to combat cancer through structure based drug designing.***

Keywords: Oral cancer, drug targets, MYC, CXCL1, XIAP.

I. INTRODUCTION

Oral malignancy is a frequent disorder in human. In India it has ranked in top three types of cancers [1]. It occurs due to heavy consumption of tobacco which contains nicotine, that leads to co-ordinate alterations by oxidative enzymes and further that leads to poor generation of electrons into an agent to be covalently bound to the DNA, generating an adduct mutated region [5]. Cigarette smoke weakens immunity in the oral cavity by promoting oral cancer [6]. Alcohol leads to increase in permeability of oral mucosa that dissolve lipids components of the epithelium, which leads to epithelial atrophy, genotoxicity and mutagenesis and interference in DNA synthesis and repair [7].

MYC (MYC proto-oncogene, bHLH transcription factor) is a proto-oncogene and encodes a nuclear phosphoprotein that plays a role in cell cycle progression, apoptosis and cellular transformation [8]. Multiple deregulations of genes in the *MYC* module is the more aggressive phenotype of tumor development [2]. It can also interact with the pre-replicative complex and cause the activation of unscheduled and unstable replication origins, leading to long-range DNA amplification [9] [10] [11]. CXCL1 was derived from NOFs by exposure to OSCC cells, suggesting that senescent process of CAFs occurs in an autocrine manner in our study model. CXCL1 transform normal fibroblasts (NOFs) into senescent Cancer-associated fibroblasts (CAFs) via an autocrine mechanism [3]. It plays a role in inflammation and exerts its effects on endothelial cells in an autocrine fashion [8]. XIAP (X-linked inhibitor of apoptosis) gene encodes a protein that belongs to a family of apoptotic suppressor proteins. This protein inhibits two members of the caspase family of cell-death proteases, caspase-3 and caspase-7. Distinct gene expression patterns between carcinomas of the floor of the mouth and oral tongue cancer can be indicated by XIAP [4]. Also XIAP can affect initiator and effector caspases, and is capable of inhibiting the intra- and extra mitochondrial apoptotic pathway [12].

II. METHODS

A. Sequence Retrieval

Uniprot database provides protein sequences which are highly annotated. The pr otein sequences of MYC, CXCL1, XIAP proteins were retrieve d in FASTA format for further analysis and Uniprot IDs were saved.

B. Physicochemical Analysis

Physicochemical parameters of MYC, CXCL1, XIAP proteins were computed using ProtParam tool available in ExPASy (http://www.expasy.org). The parameters like molecular weight, theoretical pI, amino acid composition, extinction coefficient, instability index, aliphatic index and grand average of hydropathicity (GRAVY) were computed.

C. Secondary Structure Prediction

The Self-Optimized Prediction Method with Alignment (SOPMA) (https://npsa-prabi.ibcp.fr) is online tool used to predict the secondary structure of the proteins. SOPMA predicts secondary structures of proteins such as alpha helix, beta sheets, extended strands based on its primary sequences. The secondary structures of MYC, CXCL1, XIAP proteins were predicted by using SOPMA.

D. 3D Structure visualization

RasMol is a structure visualization program for molecular graphics visualization. The 3D structures of MYC, CXCL1, XIAP proteins were visualized by using RasMol, showing different features and labels.

E. Protein Interactions

STRING (Search Tool Retrieval of Interacting Genes/Proteins) (http://string-db.org/.) is a biological database and web resource for prediction of protein–protein interactions. The interacting network of MYC, CXCL1, XIAP proteins were developed by using STRING database.

F. Domain Identification

Pfam (Protein Families) (https://pfam.xfam.org/protein/) is a collection of protein domains and families, characterized as multiple sequence alignments and as profile hidden Markov models. Conserved domains of MYC, CXCL1, XIAP proteins were predicted by using Pfam database.

III.RESULTS

A. Sequence Retrieval

Sequences of MYC, CXCL1, XIAP proteins were retrieved by UniprotKB database and stored in FASTA format with accession numbers - MYC: P01106, CXCL1: P09341, XIAP: P08170.

B. Primary Analysis

Physicochemical parameters of all these three proteins were analysed by using ProtParam tool which are as shown in table I.

TABLE I: shows physicochemical analysis of proteins

	MYC	CXCL1	XIAP
Number of Amino acids	439	107	497
Molecular Weight	48804.08	11301.42	56684.87
Theoretical pI	5.33	10.46	6.22
Total no. of negatively charged residues Asp+Glu	64	4	63
Total no. of positively charged residues Arg+Lys	51	15	58
Instability index(II)	92.23	57.92	42.63
Aliphatic index	66.42	110.47	65.35
GRAVY	-0.079	0.079	-0.541

C. Secondary Structure Prediction

Secondary structure of MYC, CXCL1, XIAP were predicted by using SOPMA tool. Secondary structural elements were listed in table II.

TABLE II: shows secondary structure prediction of proteins

	MYC	CXCL1	XIAP
Alpha helix(Hh)	32.64%	46.73%	31.79%
310 helix(Gg)	0.00%	0.00%	0.00%
Pi helix(Ii)	0.00%	0.00%	0.00%
Beta bridge (Bb)	0.00%	0.00%	0.00%
Extended strand(Ee)	12.07%	13.08%	10.26%
Beta turn(Tt)	4.33%	11.21%	44.23%

D. 3D Structure Visualization

RasMol is a 3D structure visualization program for molecular graphics visualization which shows the structures with different parameters by using different commands. The predicted 3D structure of MYC, CXCL1, XIAP proteins are as follows:

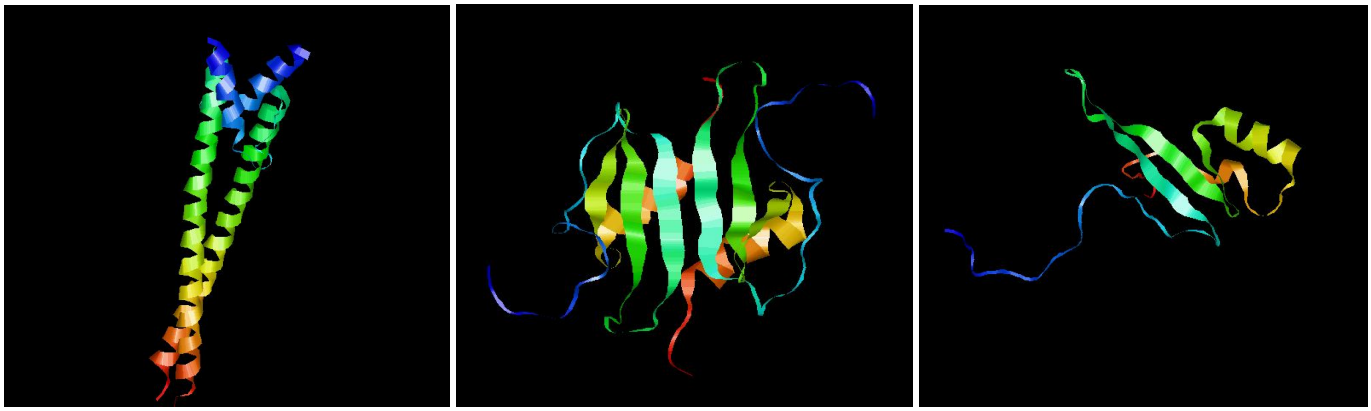

Fig 1: Showing 3D structures of MYC, CXCL1 and XIAP proteins respectively

E. Intermolecular Interaction Of Proteins

Protein-protein interactions of MYC, CXCL1, XIAP proteins were visualized using STRING database that shows the intermolecular interaction of all these proteins with other proteins as shown in figure 4.

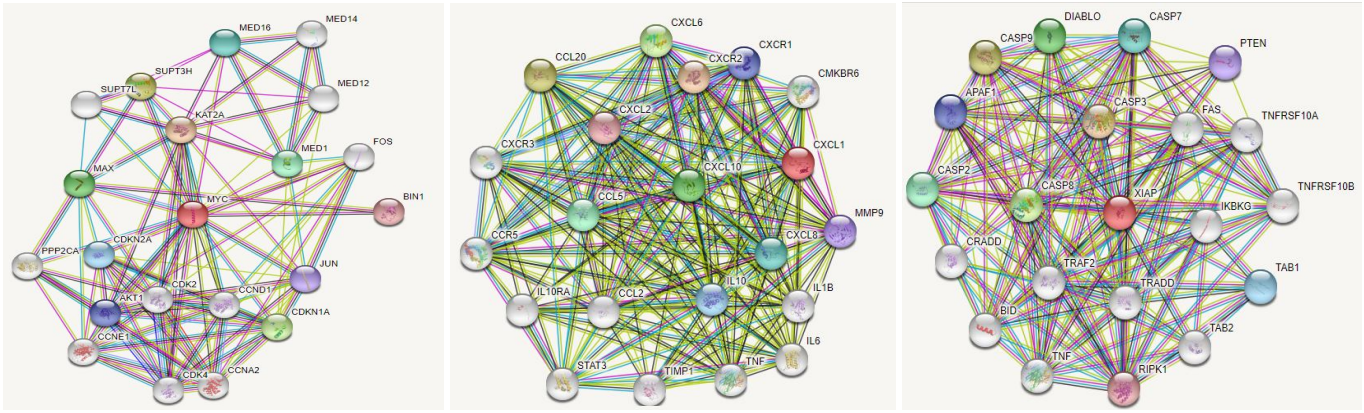

Fig 2: Showing interacting networks of MYC, CXCL1, XIAP proteins respectively

F. Domain Analysis

Conserved functional sequences of MYC, CXCL1, XIAP proteins are explained as follows by using Pfam tool.

TABLE III: shows domain identification of MYC protein

Family	Description	Entry type	Envelope		E-value
			Start	End	
Myc_N	Myc amino-terminal region	Family	1	345	1.9e-134
HLH	Helix-loop-helix DNA-binding domain	Domain	355	407	3.3e-14
Myc_LZ	Myc leucine zipper domain	Family	408	438	1.3e-15

Fig 3: shows domain identification of MYC protein in diagrammatic fashion.

TABLE IV: shows domain identification of CXCL1 protein

Family	***Description***	***Entry type***	***Envelope***		***E-value***
			Start	End	
IL8	Small cytokines (intecrine/chmokine), interleukin-8 like	Domain	41	100	1.5e-14

Fig 4: shows domain identification of CXCL1 protein in diagrammatic fashion.

TABLE V: shows domain identification of XIAP protein

Family	***Description***	***Entry type***	***Envelope***		***E-value***
			Start	End	
BIR	Inhibitors of Apoptosis domain	Domain	29	94	4.7e-19
BIR	Inhibitors of Apoptosis domain	Domain	166	231	1.2e-22
BIR	Inhibitors of Apoptosis domain	Domain	268	331	9.4e-18
Zf-C3HC4_3	Zinc finger, C3HC4 type (RING finger)	Domain	446	490	8.7e-13

Fig 5: shows domain identification of XIAP protein in diagrammatic fashion.

IV. CONCLUSION

Mortality rate in human is increasing progressively because of oral cancer. Multiple deregulations of MYC, CXCL1, XIAP proteins occurs in oral squamous cells that leads to unscheduled events in the cell. The outcomes of present investigations deal with the detailed understanding of structural and functional elements of three major drug targets with their basic physicochemical properties which states that MYC protein has low hydrophobicity, more alpha helix and single domain with two families. CXCL1 has greater hydrophobicity, more alpha helix and single domain. XIAP has low hydrophobicity, more alpha helix and four domains. These preliminary investigations can contribute to uncover the specific molecular functions of these drug targets and pave a new dimension to combat cancer through structure based drug designing.

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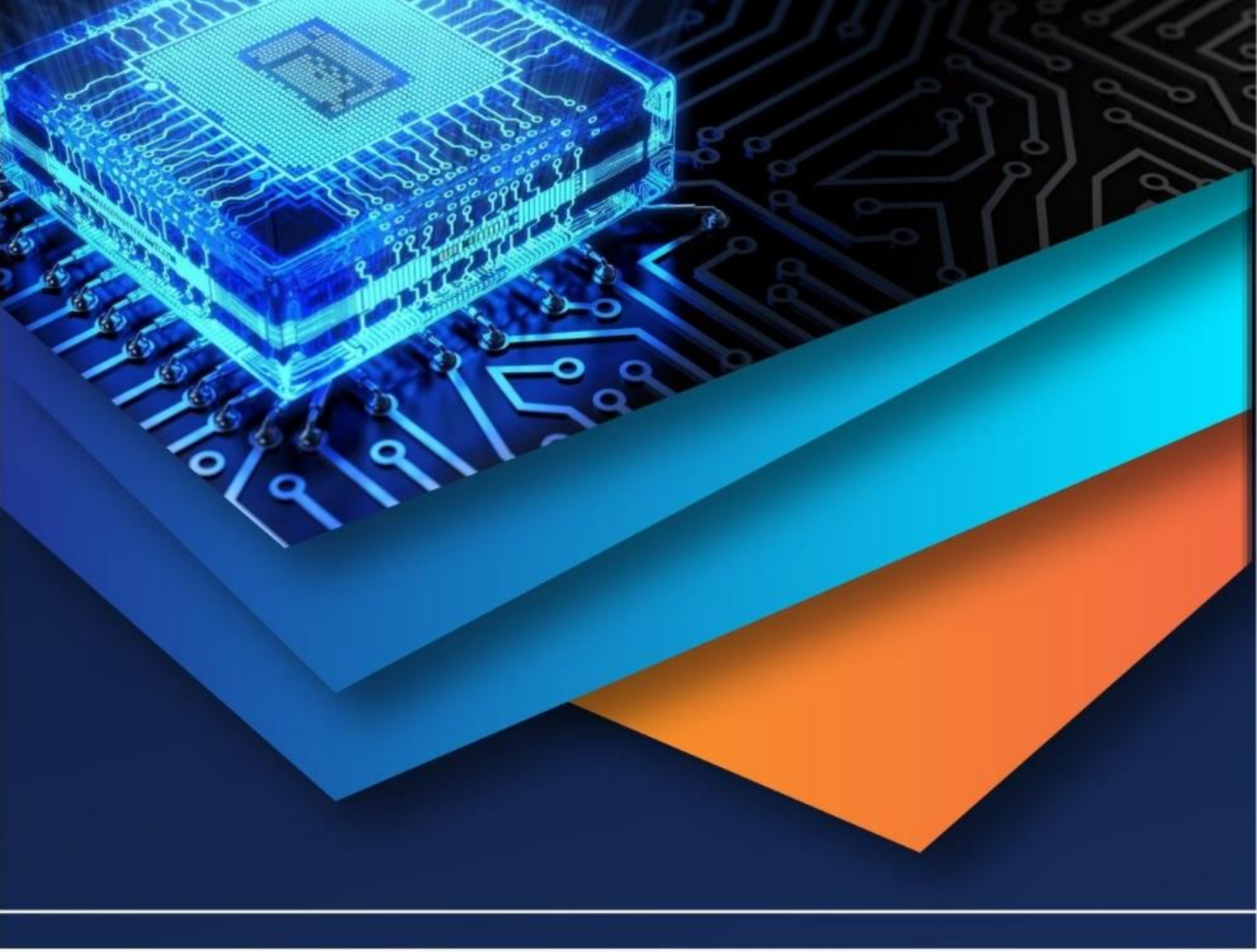

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