iJRASET
International Journal For Research in
Applied Science and Engineering Technology

# INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

**Volume:** 7 **Issue:** III **Month of publication:** March 2019

**DOI:** http://doi.org/10.22214/ijraset.2019.3007

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
*ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 6.887*
*Volume 7 Issue III, Mar 2019- Available at www.ijraset.com*

# Insilico Molecular Characterization of Potential Drug Targets in Oral Cancer

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***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:

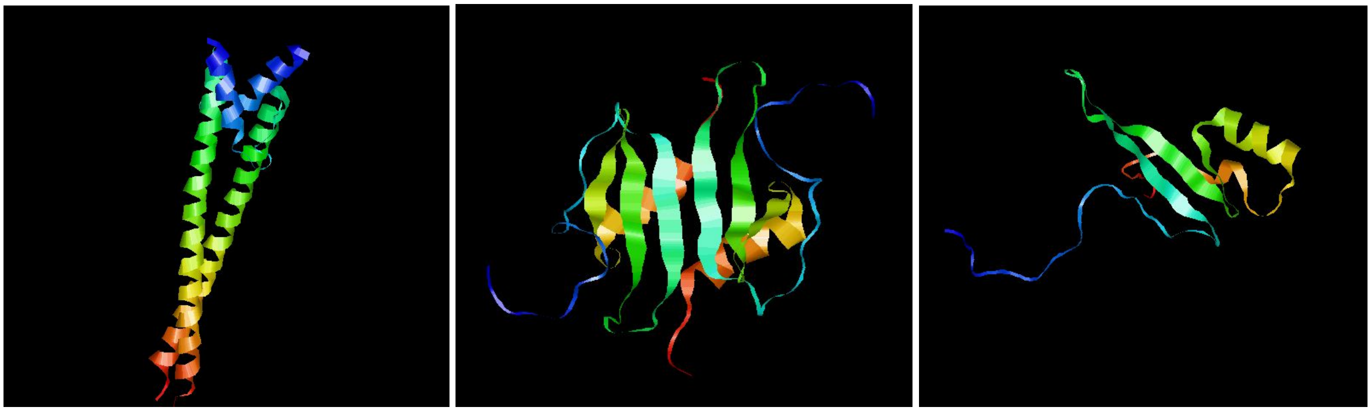

Fig 1: Showing 3D structures of MYC, CXCL1 and XIAP proteins respectively

### *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.

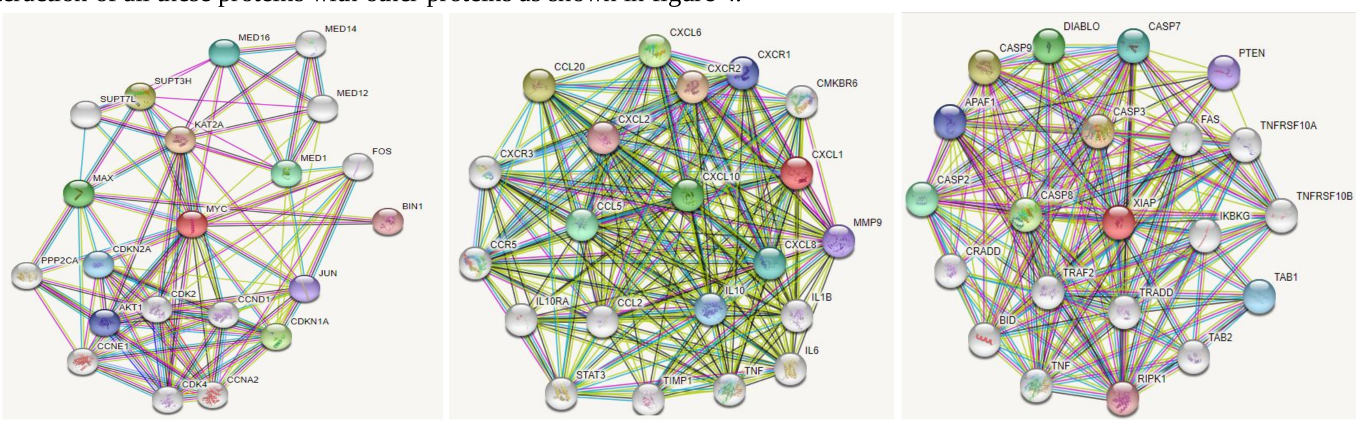


Fig 2: Showing interacting networks of MYC, CXCL1, XIAP proteins respectively

### *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 |

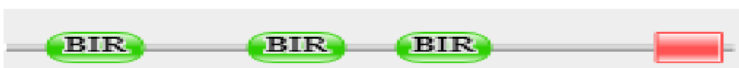


Fig 5: shows domain identification of XIAP protein in diagrammatic fashion.

## 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.

## V. ACKNOWLEDGMENT

Our sincere thanks to respected Principal of our college for providing us with all the facilities to carry out this work. We are thankful to the Coordinator, Dept. of Biotechnology for his kind support and encouragement. We are also grateful to all the faculty members of Department of Bioinformatics and Biotechnology for their proper guidance and encouragement, thanks are also due towards our parents and friends for their constant motivation and moral support throughout the work.

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