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Impact of Computers on Structural Biology of Proteins

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ABSTRACT: As more genome sequencing projects are underway on a large scale, more protein sequences are obtained and analysed. The modular units termed protein domains, associate in different ways giving rise to proteins of varied function. In the process of evolution, these combinations have produced many proteins that have new or modified functions. Thus, multidomain proteins are studied to understand the specific or more complex functions. Mutation of the domains potentially reveal disruptions of protein function which is necessary for cancer development.

I. INTRODUCTION

Proteins are composed of evolutionary units called domains; the majority of proteins consist of at least two domains. The domains and their sequences are stored in a Structural Classification Of Proteins (SCOP) database . Domains that have a common ancestor based on sequence, structural and functional evidence are grouped into superfamilies. There are more than 1200 domain superfamilies in the database[1].

Some of the few highly abundant superfamilies, for example, the P-loop NTP hydrolases, their domains and nature of their interactions determine the function of the protein. The roles that combinations of domains play in the formation of the protein repertoire have been found by analysis of domain assignments. Additional findings on the geometry of domains have been gained from examination of three-dimensional protein structures.

Different organisms have various domain repertoires. The domains can be relatively similar or there may be different domain combinations. The variability of number of different domain architectures is related to the organism complexity and lifestyle . In fact, the emergence of animals and vertebrates has been associated with the appearance of novel domain combinations. Some domain may have the capability to combine with other domain which is referred as domain promiscuity.

II. APPLICATION OF PROTEIN DOMAIN INFORMATION

Protein domains also have the ability to bind to small molecules, hence may be targets for biologically important ligands including potential drugs. An *in silico* approaches is used to detect potential candidate drug targets, using information coming from different public resources and databases.

Evolutionary domains: Proteins can combine in various ways giving rise to new domain combinations. It may give rise to new functions for the organism and the protein is referred to as evolved. Exclusive domains and domain architectures have been discovered in many species and genus of various life forms. Various software tools are used for analysis of the proteins domains and its evolution [2].

Computers have been used to predict individual structures (modelling) and intermolecular complexes (docking) and the speed, precision and accuracy of these predictions is constantly increasing. Computer predictions, however, are not always accurate, so it is important to experimentally validate them. The goal is a concerted effort by different branches of the life sciences such as biology and informatics to validate the computer predictions.

The goal is to merge experimental and computational data and to apply it to biologically relevant cases. Examples

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include interactions between antibodies and pathogens or between cytokines which are proteins responsible for biological signalling.

III. DOMAIN ANALYSIS OF ZN METALLO-BETA-LACTAMASE

Intelligent strategies have been evolved by bacteria to evade the antibiotic action and develop resistance to the action of antibiotics. The domain of Metallo- β -lactamases (MBLs) has been used as defense strategies of bacteria against β -lactam antibiotics. β -Lactam antibiotics are the most widely used antibiotics, and the major cause of resistance to β -lactam antibiotics is the presence of β -lactamases, enzymes that inactivate β -lactam antibiotics by hydrolyzing the β -lactam bond in those drugs [3-6]. MBLs hydrolyze the C-N bond of the β -lactam ring of these compounds using protein-bound zinc ions as cofactors. Their emergence in pathogenic bacterial strains and their broad substrate profile make them clinically important. Oelschlaeger and co-workers created an automated database, Metallo- β -lactamase Engineering Database (MBLED), for MBL sequences[6].

IV. DISCOIDIN DOMAIN RECEPTORS : KEY ROLE IN CANCER PROGRESSION

A fundamental characteristic of metastatic cancers is the ability of tumor cells to acquire an invasive phenotype and disseminate to other organs. The acquisition of this malignant phenotype by domain variation leads to disruptions in the physiological interactions of tumor cells with their immediate microenvironment represented by the surrounding extracellular matrix. Discoidin I functions as a lectin (a carbohydrate binding protein), playing a role in cell cell aggregation and have been found to bind to various types of collagens[8].

V. COMPUTATIONAL STRUCTURAL BIOLOGY

Homologous domains comparison are carried out for multidomain homology identification. Several schemes for scoring the homology of a pair of protein sequences have been devised [9]. To determine the function of newly discovered proteins, the annotations are transferred from well-characterized homologous proteins. Homologous proteins are then screened from sequence-based and domain-based approaches. Domain-based methods have several advantages for identifying distant homology and homology among proteins with multiple domains.

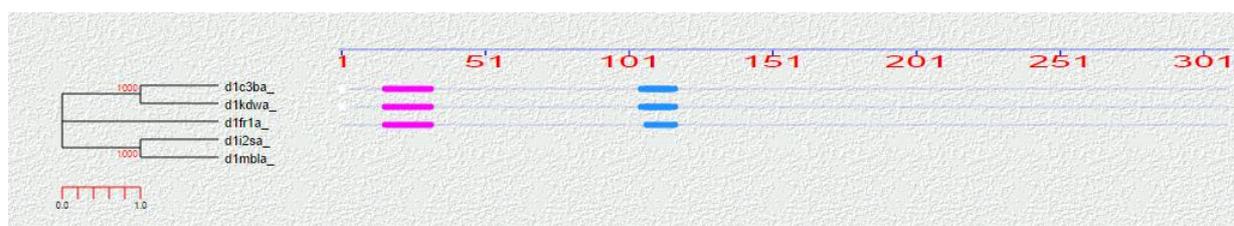


Fig1: Output from TreeDom viewer showing metallo lactamase domains from bacteria.

VI. CONCLUSION

Computational domain analysis provide an insight into protein function. Multidomain analysis by homology identification provide annotation of protein function which may be obtained from well characterized proteins.

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