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Research and development status of antifungal drugs based on proteomics

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Abstract. Invasive fungal infection has become one of the serious threats to human health. There is an urgent need to develop a new and efficient antifungal drug. In this study, we mainly conducted a literature survey in the field of proteomics in the research and development of antifungal drugs, summarized the current situation of proteomics in the research and development of antifungal drugs from Aspergillus fumigatus and Candida albicans, and pointed out the shortcomings of the current research. This study will summarize the previous research results and methods, and guide the research in this field with AI based protein prediction technology.

Keywords: Proteomics, Antifungal Drugs, Candida Albicans, Aspergillus Fumigatus.

1. Introduction

Invasive fungal infection has become one of the serious threats to human health. The broad-spectrum antifungal prevention measures have reduced the incidence of patients with traditional risk factors and improved the survival rate of patients [1], but some rare fungal pathogens and some drug-resistant strains have become resistant to existing drugs [2], therefore, it is urgent to develop a new and efficient antifungal drug. Through the investigation of existing research, it is found that the current research mainly focuses on the application of quantitative proteomics technology in antifungal drugs, such as non-standard quantitative, standard quantitative and proteomic database. These methods have the disadvantages of low efficiency, long cycle and high sample requirements in the research and development of antifungal drugs, these shortcomings can be improved in AI based protein structure prediction technology. However, few people use AI based protein prediction technology in antifungal drugs. In order to improve the efficiency of antifungal drug research and development, save research and development costs and shorten the research and development cycle, this study will summarize the previous research results and methods, and guide the research in this field with AI based protein prediction technology. This paper first analyzed the principle of proteomics, then discussed the current situation of proteomics in the research and development of antifungal drugs from Aspergillus fumigatus

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and Candida albicans, and finally prospected the application of new proteomics methods in antifungal drugs.

2. Proteomics technology

Proteomics technology has become one of the important means in the field of new drug development after continuous development in recent years. The new antifungal drug development research using proteomics technology has been on the rise in the past 15 years (FIG 1). Protein is the final product of gene expression and the main carrier of biological structure and function. Proteomics is the separation and determination of all proteins on a large scale, and the analysis of protein expression, post-translational modification, protein-protein interactions, etc [3]. In the application of antifungal drugs, most of them are quantitative proteomics. Quantitative proteomics technology can be divided into three types: non-standard quantitative, standard quantitative and absolute quantitative.

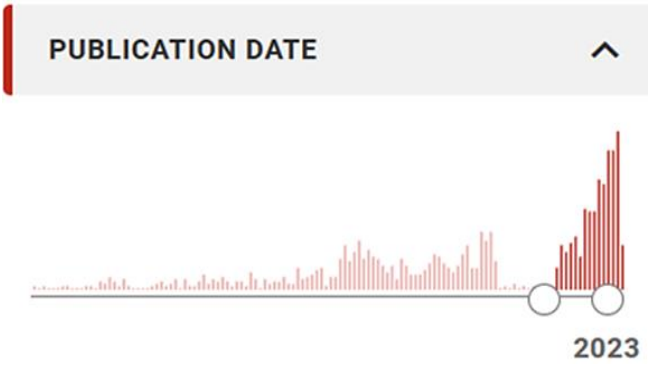

Figure 1. The number of articles related to proteomics and fungi from 2008 to 2022 retrieved by advanced search on science website.

2.1. Nonstandard quantitation

The calculation methods of standard free quantification can be divided into two categories according to the principle. The first category is the quantitative algorithm of Xic, which is divided into two methods: (1) matching with the accurate mass and time tag (AMT) database [4]. (2) using the search results of protein sequence database, determine the corresponding peptide sequence. The second type of standard free quantitative method is spectral counting (SC) according to the principle that the higher the protein abundance, the greater the probability that the corresponding peptide will be detected by mass spectrometry, this method defines the number of corresponding identification spectra (PSM) of a protein as the relative abundance of the protein [5].

2.2. Standard quantitation

Standard proteomics has been widely used in biological research, precision medicine, drug discovery and other fields, and is a hot research direction of proteomics [6]. In the same spectrum, different labeled peptides will form isotope peaks with poor fixed mass. Based on this information, the kurtosis information and corresponding ratio of the same peptide in each labeled state can be calculated. The latest tandem mass tag (TMT) can achieve up to 18-fold labeling, coupled with the use of high-resolution mass spectrometer, it has become a reality to accurately quantify the expression changes of the same protein in a variety of cell states on a large scale [7]. Lucía Citores et al [8] used a high-resolution lc-ms/ms method based on tandem mass spectrometry (TMT) to differentiate the antifungal drugs produced by organisms.

2.3. Proteomic prediction technology based on AI

Recently, alphafold2, a deep neural network-based machine learning application, can predict unknown protein structures with unprecedented accuracy [9]. John jumper et al [10] provide a computational method called AlphaFold2 which can forecast the structure of protein and have the highest accuracy

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compared with other types of computational method in the challenging 14th Critical Assessment of protein Structure Prediction (CASP14). What's more, AlphaFold2's accuracy reaches atomic level even in cases in which no similar structure is known which is a great science breakthrough and can significantly enhance the efficiency and reduce research and development time in drug development.

Alphafold2 has unparalleled efficiency in protein structure prediction. Compared with traditional proteomics technology, alphafold2 has low sample requirements and fast prediction speed. It can greatly shorten the cycle of drug research and development. What's more, it also can reduce the cost of drug research and development, which is the frontier direction of proteomics.

3. Application of proteomics in research and development of antifungal drugs

Fungi are a kind of monocyte organisms widely existing in nature. There are more than 300000 kinds of fungi, of which about 600 are related to human diseases. At least 1.35 million people worldwide die from fungal invasion every year [11]. Clinically, Aspergillus fumigatus (mortality 50% -90%), Cryptococcus neoformans (mortality 20% -70%) and Candida albicans (mortality 20% -40%) are considered to be the three most important pathogens causing fungal infections [12]. Nowadays, with the increase of fungal resistance, antifungal drugs are not enough to deal with the harm of fungi to human beings. Therefore, it is necessary to develop new antifungal drugs, and the application effect of proteomics in the field of drug development is obvious. The existing research results show that proteomics can play a key role in the development of antifungal drugs.

3.1. Candida albicans

Nowadays Candida albicans have an increase trend which is infected humans. Now, due to factors such as broad-spectrum antibiotics and organ transplantation, Candida albicans has shown resistance in clinic, which mean developing a new type of drug is necessary. Long Bing Yang et al [13] explained the mechanism of action of a new antimicrobial peptide amp-17 by using TMT Technology, they using the AMP-17 to treated the Candida albicans and performed Proteomics analysis of it. Overall, 3931 proteins were identified, of which 3600 contained quantitative information. In AMP-17/control 423 differential expressed proteins (DEPs) were upregulated and 180 DEPs downregulated, Research has shown that the antifungal mechanism of AMP mainly leads to cell damage by affecting the synthesis of related genes such as microbial cell membranes, cell walls, etc. It providing some technical support and theoretical basis for the development of new peptide drugs. Gbala ID et al [14] used two recombinant amp actifensin and defensin-d2 to act on Candida albicans and performed proteomic analysis. A total of 9 differentially expressed proteins (DEPs) were identified in the treated C. albicans, respectively. There are 5 (83.3%) proteins downregulated in defensin-treated P. aeruginosa, while4(80%) were downregulated in actifensin-treated C. albicans (ACA). Functional analysis shows that DEPs were involved in phosphorus oxidation, RNA decomposition, and energy metabolism in Candida albicans. It is pointed out that two antimicrobial peptides (AMPS) have strong membrane destruction and antifungal effects on Candida albicans.

The current research shows that the application of proteomics in the research and development of anti-Candida albicans drugs is effective and potential, but there are few related studies, and the depth of exploration of new drug targets and protein drugs is not enough. The traditional proteomics technology has the disadvantage of low efficiency in the development of anti-fungal drugs, However, AI based proteomics can do better in drug discovery.

3.2. Aspergillus fumigatus

Aspergillus fumigatus has a very high mortality rate in people with low immunity, so the drug treatment of Aspergillus fumigatus is particularly important. However, with the factors of drug abuse in recent years, the drug resistance of existing drugs has gradually increased, and new drugs need to be developed. The use of proteomics for drug research and development has been proved to be efficient in existing studies. At present, the application of proteomics technology in anti-Aspergillus fumigatus drugs is rare, but the high mortality rate of Aspergillus fumigatus in clinic cannot be ignored. The development of

anti-Aspergillus fumigatus drugs using proteomics technology can make the drug development process more efficient and shorten the development time. Researchers should pay attention to the application of proteomics technology in anti-Aspergillus fumigatus drugs.

4. Conclusion

In the current research, most researchers use traditional protein analysis technology, which has the disadvantages of high sample requirements, high cost, long cycle and so on. However, protein prediction based on AI has excellent prospects, with many advantages such as low sample requirements and low cost. It is promising and has great potential to develop antifungal drugs by using new proteomics technology. For example, the structure predicted by alpha fold introduced in this study provides the entrance of many new protein targets for structure-based drug design. In the future, with the rapid development of AI technology, there will be more and more excellent algorithms of AI based proteomics technology. In the field of the application of proteomics technology in the research and development of antifungal drugs, AI can improve the efficiency of this field and discover new and efficient drugs faster.

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