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Original Article

A Systems Biology Analysis of *Aspergillus fumigatus* Genome Exhibits Specific Gene Expression Patterns in Exposure to Human Blood Platelets

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Abstract

Introduction: *Aspergillus fumigatus* is an opportunistic filamentous fungus and is currently the most frequent cause of invasive aspergillosis, being the most common life-threatening opportunistic invasive mold infection in immunocompromised individuals. Understanding the genetic expression patterns of pathogens during feeding provides key insights for addressing such phenomena. As a complex nutrition source containing lipids, amino acids, and nucleotides, platelets appear to be a rich food source for microorganisms.

Materials and Methods: Using systems biology approaches, this study investigated the primary genes responsible for *Aspergillus fumigatus* behavior alteration during platelet exposure. The genes and corresponding modules were identified based on weighted gene co-expression network analysis.

Results: Differential Gene Expression analysis studies revealed that nine genes were downregulated, while 60 genes were upregulated. Weighted Gene Co-expression Network analysis identified non-preserved gene modules that showed highly altered genes over time steps. Gene Ontology studies based on Weighted Gene Co-expression Network analysis indicated that significant alterations occurred in molecular biological processes, including glycine, serine, and threonine metabolism, aminoacyl-tRNA biosynthesis, ABC transporters, RNA transport, ubiquitin-mediated proteolysis, transmembrane transport, and carbohydrate metabolic processes.

Conclusions: Our functional analysis highlighted a new research direction in the systems biology of *Aspergillus fumigatus*. This insight into invasive aspergillosis could also guide researchers towards novel platelet-based therapies involving molecular interventions.

Keywords: WGCNA, *Aspergillus fumigatus*, Platelet, Differentially Expressed Genes, Systems Biology

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Introduction

Aspergillus fumigatus is a ubiquitous environmental filamentous fungus that releases numerous small conidia into the air. Inhalation of *A. fumigatus* conidia can cause a wide range of clinical manifestations, such as life-threatening Invasive Aspergillosis (IA) in immunocompromised patients. A significant increase in IA cases has been reported in recent decades, primarily due to medical interventions such as chemotherapy and immunosuppression. Additionally, there is a lack of reliable diagnostic tools and effective treatment options for severe cases of IA, resulting in a high mortality rate despite therapy.[1] Notably, *A. fumigatus* is responsible for 90% of all systemic aspergillosis infections. This opportunistic pathogen possesses certain virulence factors and is considered as one of the primary causative agents of IA.[2] Furthermore, there is a significant correlation between immunosuppression rates and the severity of IA.[3]

Recent studies have analyzed the molecular aspects of *A. fumigatus* and have led to the availability of its genome sequence.[2-4] However, only a few virulence factors of *A. fumigatus* have been determined to date. These factors include the siderophore-mediated iron uptake system,[5] the *pksP* gene, which is involved in the biosynthesis of spore pigmentation,[5-7] and Dihydroxy Naphthalene Melanin (DHN), which is shown to prevent apoptosis and acidification of phagolysosomes in macrophages.[6,7] In addition, *A. fumigatus* can contribute to mechanisms of immune escape that decrease recognition by immune cells and the complement system.[8,9] Innate immunity is one of the most critical forms of protection against *A. fumigatus*. Alveolar macrophages are the primary cells in the lung alveoli that play an essential role in removing fungal conidia from the lung.[6,10,11] However, non-phagocytosed conidia and hyphae germinating from conidia are killed by neutrophils, whose activity is critical for preventing IA.[12] Moreover, the complement

system plays a vital role in the defense against *A. fumigatus*.[13] Human pattern recognition receptors such as Toll-Like Receptors (TLRs), Galectin 3, DC-Sign (C-type lectin receptors), Dectin-1, SCARF1, and CD36 can recognize fungal cell wall components. Dectin-1 is an essential receptor on macrophages and neutrophils, and the surface of immature DCs can induce pro-inflammatory cytokine production.[14] Additionally, neutrophils have been shown to form neutrophilic extracellular traps (NETs) as extracellular killing mechanisms against *A. fumigatus*.[15,16] Phagocytosis of conidia by DCs leads to a protective Th1 response, while hyphal phagocytosis triggers an undesirable Th2-type immunity and induces CD4 cells to produce IL-10.[17] Overall, innate and adaptive site-specific immunity contribute to the host defense against *A. fumigatus*.[18,19] Moreover, platelets play important and multifaceted roles in antibacterial host defense.[20-22] Only a few data on the antifungal functions of platelets against *Aspergillus* are presented.[10,23] It is revealed that germination and hyphal elongation of *Aspergillus* are considerably affected when treated with platelets. Additionally, the polysaccharide galactomannan, a primary structural component of *Aspergillus* species, significantly decreases after platelet exposure.[23] Studies on the transcriptional response of *Aspergillus* spp. exposure to human cells are limited. Genes differentially expressed in *A. fumigatus* after exposure to neutrophils, monocyte-derived dendritic cells, airway epithelial cells, and platelets have been studied recently.[24-28] In this study, we aim to investigate the main genes responsible for the alteration of behaviors of *A. fumigatus* during exposure to platelets as a complex nutrition source that contains lipid content, amino acids, and nucleotides in different forms of RNA. Identification of the genes and corresponding modules based on Weighted Gene Co-expression Network Analysis (WGCNA), a complex systems biology approach to identify genes acting in the same group despite not being differentially expressed.

Materials and Methods

To acquire the necessary interaction data between platelets and *A. fumigatus*, various databases, including GEO and ArrayExpress, were searched using different keywords. The microarray dataset E-MTAB-3024 was obtained and sequenced on the ZINF/Krappmann_14k_v1 Platform. This dataset included control samples and samples taken at 15 min, 30 min, 60 min, and 180 min after treating *A. fumigatus* with platelets. Each stage consisted of three samples.

All probes were analyzed before annotation procedures to minimize data loss. The Limma package in R was used to identify differentially expressed genes (DEGs) in various stages of the study after log2 transformation and data normalization.[29] The *p*-value was adjusted according to FDR <0.05 and log2 fold change >2. Gene Ontology (GO) analysis was carried out on DEGs to identify the cellular components, molecular functions, and biological processes associated with genes.

To investigate the interaction of genes as a whole deeply, gene co-expression networks were considered in all stages of the study solely and in comparison with each other. The WGCNA package in R was utilized to analyze the time series data[29,30] to achieve the goal. The parameters of WGCNA analysis for each set of data were related to network type (signed), Cytoscape threshold (0.8), minimum module size,[30] clustering method (average), and module depth.[3]

Module preservation analysis was carried out to identify the differences between genes moving between modules, meaning the gene changes behavior from one sample to another. In this analysis, all time-series modules were given a score (Z-score) that defines the amount of preservation of the probes inside. Modules with Z-scores lower than five were subjected to further analysis. After acquiring the low-preserved modules, the internal probes were transformed into the original Entrez ID by the DAVID online tool (https://david.ncifcrf.gov/) for further analysis with the GO tools of the same website.[30]

Results

DEG analysis studies determined that nine genes were downregulated and 60 genes upregulated. Some of the main dysregulating genes included Asp-F13, endopeptidase Pep1, and endo-1,3-beta-glucanas. A heatmap of the samples is visible in Figure 1, showing specific pattern changes among samples and series. It is observable that DEGs were slowly upregulating during the induction with stimuli. However, upregulation patterns merely disappeared 180 min after treatments.

The scale independence and mean connectivity of all groups were calculated to identify the possibility of generating a natural biological network. The scale independence and mean connectivity of the control group are shown in Figure 2.

After identifying ß as the soft threshold (power) for the analysis based on scale independence, modulation analysis was applied at all stages to assort the probes into different modules. Figure 3 displays the color dendrogram of the control group, illustrating gene modulation based on calculated distances between genes of control group samples. Various modules can be visually identified in this figure.

To visually identify the real-time differences between different stages of the study and modulation of the genes, a hybrid dynamic tree and gene dendrogram of all stages based on control samples were drawn and studied carefully. Figure 4 demonstrates the mentioned graph for control and 15-minuts groups. Different modulation patterns are visible in the colored rows of the figure. Each color represents a specific module in different sets of samples.

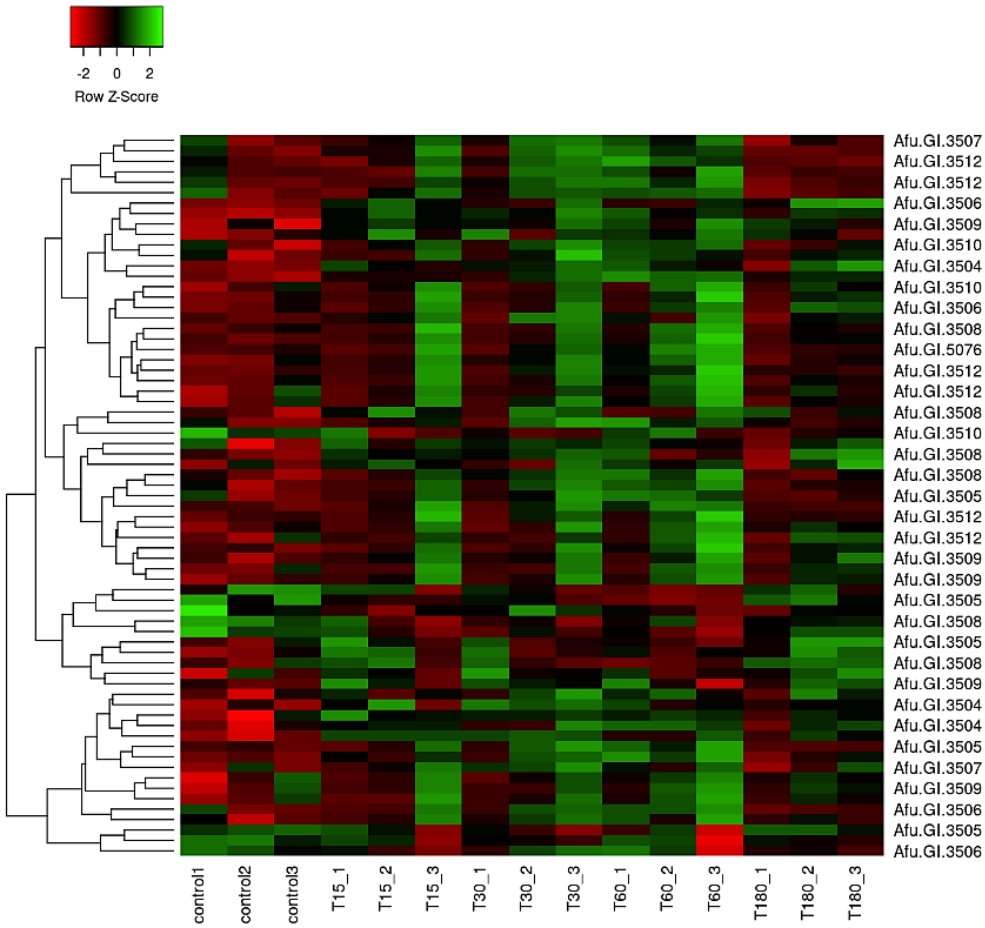

Figure 1. Heat Map of Z-scores of Different Modules in Different Treatment Times Compared with the Control. Specific pattern changes among samples and series through the heat map can be observed.

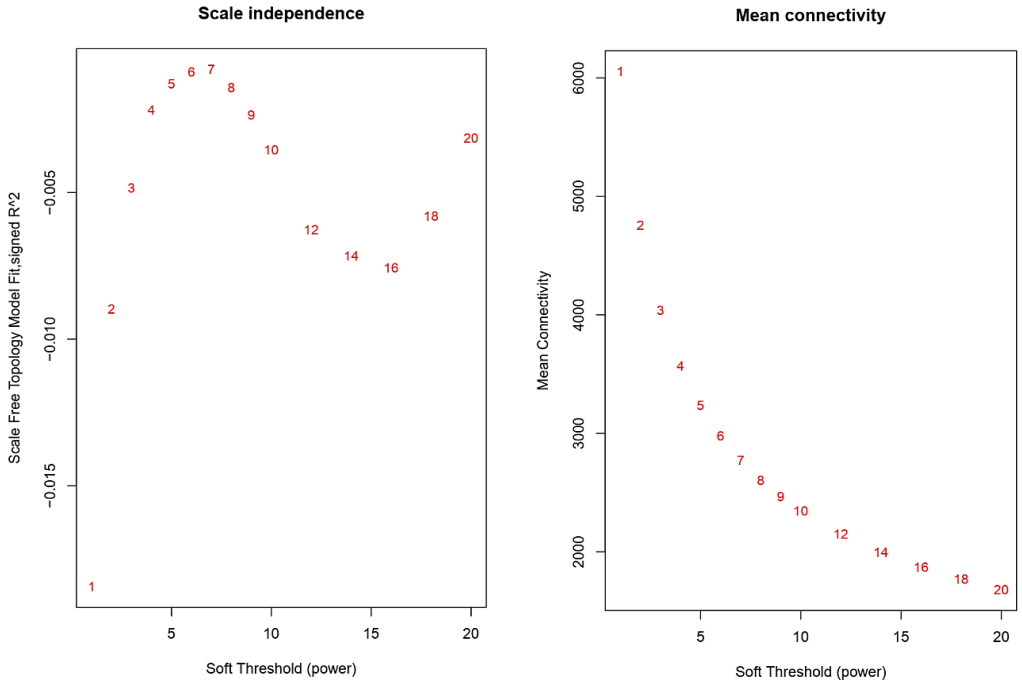

Figure 2. Scale Independence and Mean Connectivity of the Control Group to Identify the Soft Threshold. The scale independence graph demonstrates the power in which the data complies with the Power Law. The mean connectivity graph shows the average number of connections for all nodes in the co-expression network at the chosen soft threshold.

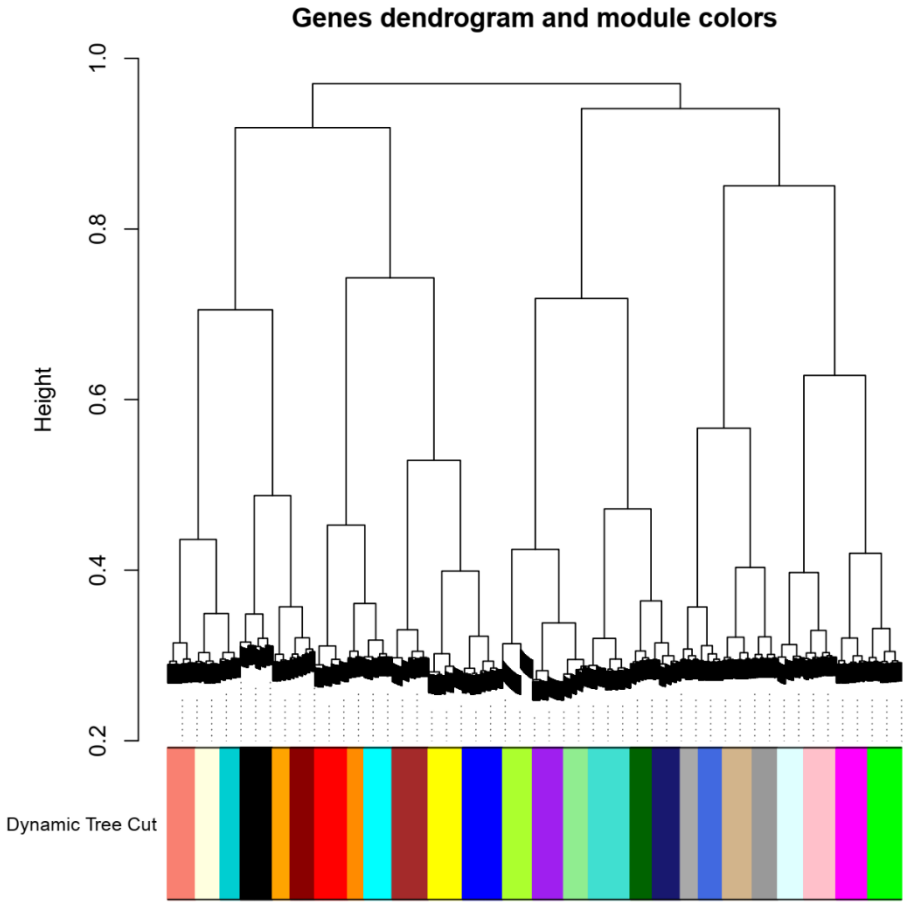

Figure 3. Dendrogram and Gene Modulation of the Control Group. Different sets of genes are accommodated in different modules represented with different colors. These genes possess a similar behavior in co-expression network. The dendrogram demonstrates the closeness tree of the modules and included gene.

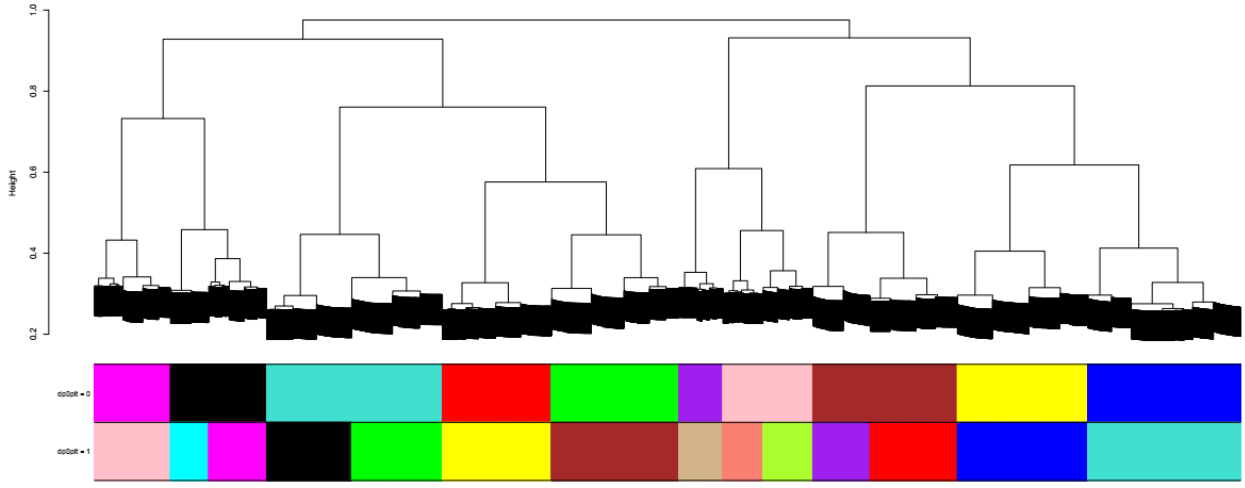

Figure 4. Dendrogram and Gene Modulation Comparison of the Control and 30 min Group. Up and down modules belong to control and 30 min treatment groups, respectively. The divergent co-expression of the genes is visible in the lower modulation. This divergence is due to the present stimulation that induces the new genes to express differently.

Z-scoring studies among modules are presented in Table 1. It is evident that different modules of genes are not conserved across different stages of the study. These genes were not necessarily differentially expressed genes (DEGs), but they exhibited similar behavior in various stages of the study. Genes must adhere to specific statistical rules for *p*-

value and false discovery rate (FDR) calculations to be classified as DEGs, but WGCNA categorizes genes using similar approaches. Modules with a Z-score lower than five can be referred to as low-preserved modules, which essentially contain genes exhibiting similar behavior in specific sample groups but varying significantly between different stages.

Table 1. Z-scoring of the Modules Compared between Time Series with Original Control Time

Control vs. 15 min			Control vs. 30 min			Control vs. 60 min			Control vs. 180 min		
Module	**Size**	**$Z_{summery}$**	**Module**	**Size**	**$Z_{summery}$**	**Module**	**Size**	**$Z_{summery}$**	**Module**	**Size**	**$Z_{summery}$**
Red	679	34.89174477	yellow	1000	18.85784	gold	1000	11.88043	gold	1000	40.17056
Gold	1000	25.12101481	blue	1000	17.95585	red	589	8.872815	yellow	1000	17.56064
Purple	547	23.9976664	gold	1000	15.16852	yellow	1000	6.789606	blue	1000	16.67772
Black	634	18.48041613	green	1000	14.70179	blue	1000	5.726607	pink	448	8.55914
Turquoise	1000	13.82176733	magenta	630	13.68821	turquoise	1000	5.279145	turquoise	1000	8.489689
Yellow	815	10.46198552	purple	367	9.141556	magenta	521	4.928224	red	602	7.786893
Green yellow	513	9.406256184	red	904	8.913703	pink	525	4.313729	magenta	436	7.017408
Blue	1000	8.670886888	pink	744	6.683987	brown	1000	3.923316	green	806	6.4793
Pink	623	7.662046195	brown	1000	5.09735	black	539	3.632855	brown	1000	5.961515
Tan	502	7.540332751	turquoise	1000	2.641205	green	634	2.173473	black	554	4.207608
Green	780	4.438939081	black	796	1.535257	greenyellow	361	0.907886	purple	326	0.525578

The green module, as the main module of the 15-minute group cases, can be set as the principal module. This module possesses a Z-score of 4.438939081 in calculations, which means it contains genes with the highest alterations compared to the control group. It is comprised of 780 nodes and 274160 edges. The centralization and heterogeneity of the network are 0.2 and 0.244, respectively. As it is evident, the network is highly interconnected due to the high correlation between nodes. Comparing the increasing number of modules from the 15-minute to the 60-minute group highlights the fact that the highest number of alterations in gene behaviors usually occur from the beginning of pathogen exposure to platelets until 60 min afterward. Due to the presence of only two modules with a Z-score ≤ 5 in the 180-minute group, it appears that shifts in the signaling and metabolic pathways of the pathogen are complete before 180 minutes.

Gene Ontology Classification of Differentially Expressed Genes in Modules

Following GO studies based on specified modules in the time series of the study, it was revealed that main alterations and changes were carried out in the following biological processes. Interestingly, based on predicted issues about the complex food source, different metabolic pathways of the organism were activated during different time series. Table 2 demonstrates the different biological pathways presented and expressed during different time steps.

Table 2. Gene Ontology Analysis of low Z-Score Modules

GO Category	15 min	30 min	60 min	180 min
Glycine, serine and threonine metabolism	-	+	+	-
Aminoacyl-tRNA biosynthesis	-	+	+	-
ABC transporters	+	-	-	-
RNA transport	+	-	-	-
Ubiquitin mediated proteolysis	+	-	-	-
Transmembrane transport	+	+	+	-
Carbohydrate metabolic process	+	+	+	-
Cell division	+	+	+	-
Glycolysis / Gluconeogenesis	+	+	+	-
Oxidative phosphorylation	+	+	+	-
Amino sugar and nucleotide sugar metabolism	+	+	+	-

Discussion

Microorganisms utilize different sets of proteins under varying conditions. These gene sets may show differential detectability, with some alterations being subtle and requiring specialized analysis tools for detection. Gene co-expression analysis is a crucial and complex systems biology approach that can identify changes in the behavior of gene sets. Given the limited number of samples in the current study, modified weighted gene co-expression network analysis can be employed for a more in-depth analysis of gene expression changes.

All co-expression networks must adhere to the power law rules to become natural scale-independent networks like biological protein interaction networks. Initially, changing the beta (β) variable is mandatory, as it is a determinant factor in the scale-independence calculations of WGCNA. According to the WGCNA package instructions, β must be set to 18 for studies with fewer than 20 samples.[31,32]

During the differential analysis of gene sets based on the heatmap, it was visually apparent that the expression level changes of genes were stage-dependent. Upregulation of DEGs can be traced until 60 minutes after treatment. It appears that the provided concentration of platelets as a food

source for the organism depletes after 180 minutes because identified DEGs are downregulating and returning to their average expression levels.

Some recent studies have been conducted on *A. fumigatus* using systems biology approaches. Linde et al. analyzed the entire transcriptome of *A. fumigatus* under iron depletion stress over a specific time series. They identified new candidate genes for the regulatory network involved in iron processing and stress control.[33] In another study, a network approach of gene co-expression was utilized to study the interaction between Zea mays and *Aspergillus flavus*. Following network analysis, O-methyltransferase, O-methyl sterigmatocystin oxidoreductase, and Noranthrone monooxygenase, as well as an unknown protein, were investigated as novel targets.[34] Likewise, a network modeling approach was used to study the interaction of *A. fumigatus* during adaptation to caspofungin stress.[35]

In a similar study conducted by Perkhofer et al., genome-wide identification of differentially expressed genes in *A. fumigatus* was performed after exposure to human platelets for various time points (15, 30, 60, and 180 minutes). They observed upregulation patterns more in early time points compared with 180 min after treatment. The data analysis included gene ontology annotation, functional categorization (FunCat), and KEGG enrichment analyses to understand the impact of platelets on the fungal transcriptional response. They understood that early exposure of *A. fumigatus* to platelets led to the down-regulation of RNA modification and processing-related processes, potentially reflecting the attenuation of hyphal elongation and germination induced by platelets. Additionally, oxidative phosphorylation and energy-generating processes were decreased upon platelet exposure, indicating a shift in metabolic pathways in *A. fumigatus* in response to platelets. This early transcriptional response of *A. fumigatus* to platelets sheds light on the molecular mechanisms underlying the antifungal effects of platelets and their role in host defense against fungal infections. Furthermore, the study revealed that platelets interacted with *A. fumigatus* hyphae, aggregated around the fungus, and released serotonin stored in their dense granules within 30 minutes of exposure.[36]

In our study, we investigated the regulation of 69 DEGs through gene ontology analyses. GO annotation of the DEGs identified associations with biological processes such as oxidoreductase activity, RNA processing, pathogenesis, translation, and amino acid and nucleotide metabolism. Exposure to platelets resulted in the deregulation of several genes related to zinc finger proteins, such as C2H2 Finger Proteins (AFUA_2G15110, AFUA_3G14090). Additionally, the AAA family ATPase (AFUA_7G06680) was found to be upregulated during IA infection. Consistent with our findings, other studies have shown that *A. fumigatus* interaction with human neutrophils and monocyte-derived immature dendritic cells leads to significant changes in clusters of genes involved in similar biological processes, such as transport, pathogenesis, RNA processing, and ribosome biogenesis. However, differences in gene regulation reported in these studies may be attributed to various factors, including the types of cells used.

Biological processes and pathways in Z-Score modulation studies reveal more detailed alterations of the differentially acting genes. It is evident that some pathways, such as transmembrane transport, carbohydrate metabolic process, cell division, glycolysis/gluconeogenesis, oxidative phosphorylation, and amino sugar and nucleotide sugar metabolism, were upregulated following initiation of the treatment and were downregulated after 3 hours due to the exhaustion of the food source. They are mostly related to catabolic pathways where harvesting nitrogen, phosphorus, and carbon are the main goals of such pathways.

On the other hand, other pathways, such as ABC transporters, RNA transport, and ubiquitin-mediated proteolysis, were only expressed during the first 15 min. These pathways mainly belong to the stationary phase of the growth chart, within which misfolded and inefficient proteins are being degraded, or biotoxins and other compounds must be selectively transported out of the cell. However, abundant food resources keep cells in the logarithmic growth phase, where translated and folded proteins are divided into different sister cells. Other middle-level pathways, such as glycine, serine, and threonine metabolism, or aminoacyl-tRNA biosynthesis, depend only on precursors produced by the previously mentioned pathways.[37] These pathways represent the middle of the growth procedure where there is enough flow in other metabolic pathways. This study is the only that practically investigates the ignored aspects of gene expression in *A. fumigatus* during treatment with platelets as a rich food resource.

Conclusion

According to the findings of this study, the role of platelets in aspergillosis is revealed, and further studies are warranted to clarify the overall significance of platelets in *Aspergillus* infection. Our findings delineated the possible induction of fungal pathways by platelets. This provides a new research line into *A. fumigatus*' pathogenesis. Such insight into IA pathogenesis might also guide researchers toward novel platelet-based therapies that involve molecular interventions, especially in IA patients.

This study on the interaction between platelets and *A. fumigatus* provides significant insights into the dynamic gene expression changes in response to platelet exposure. One of the key biological implications is the identification of differentially expressed genes (DEGs) and their associated biological processes, such as oxidoreductase activity, RNA processing, and pathogenesis. Understanding these processes

helps elucidate how *A. fumigatus* adapts to the presence of platelets, which can be crucial for developing targeted antifungal therapies. The upregulation of specific genes, such as zinc finger proteins and AAA family ATPases, highlights potential targets for therapeutic intervention, aiming to disrupt the pathogen's ability to thrive in the host environment. Moreover, the study's use of Weighted Gene Co-expression Network Analysis to identify gene modules and their preservation across different time points provides a deeper understanding of the regulatory networks involved in *A. fumigatus*'s response to platelets. This approach allows for the identification of key regulatory genes and pathways that are consistently altered during the interaction. The findings suggest that metabolic pathways, such as glycolysis /gluconeogenesis and oxidative phosphorylation, are initially upregulated but downregulated after the depletion of the platelet food source. This temporal regulation of metabolic pathways can inform the timing and strategy of antifungal treatments, potentially enhancing their efficacy by targeting the pathogen at its most vulnerable stages. The broader applications of this research extend to the development of novel therapeutic strategies and diagnostic tools. By identifying specific gene expression patterns and regulatory networks associated with *A. fumigatus*'s adaptation to platelet exposure, new biomarkers for early detection and monitoring of fungal infections can be developed. Additionally, the insights gained from this study can be applied to other pathogenic fungi, improving our overall understanding of host-pathogen interactions and guiding the development of broad-spectrum antifungal agents. The integration of multi-omics data and advanced bioinformatics approaches, as demonstrated in our study, sets a precedent for future research in fungal biology and infectious disease management. This study not only demonstrates the simultaneous overexpression of specific pathways during exposure to platelets but also reveals collaboration between these metabolic and signaling pathways, which could be used for further studies to design proper inhibitors for unbalancing the signaling and metabolic network of *A. fumigatus* leading to incapacitating its aggressive nature.

Authors' Contributions

Conceptualization by BA, MA, HB; Methodology, Validation, and Investigation by MA, HB; validation and Formal analyses by MA and HB; Writing-original draft preparation by BA and HB; Writing – review and editing by BA, MA, HB; Supervision by MA and HB.

Conflict of Interest Disclosures

The authors declare that they have no conflicts of interest.

Ethical Approval

The Tehran University of Medical Sciences Ethics Committee approved the protocol for this study (IR.TUMS.SPH.REC.1398.194).

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