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Comparative analysis of active networks reveals the changes of key proteins and their interactions under different oxygen levels in *Shewanella oneidensis* MR-1

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Abstract

Purpose The extracellular electron transfer (EET) capability enables electroactive microorganisms have a wide range of applications in energy production, wastewater treatment, bioremediation and chemical synthesis. Because the oxygen levels will sharply affect the EET process, we integrated transcriptome changes under different oxygen levels with protein–protein interaction (PPI) network to study the specific changes under these conditions in a typical electroactive microorganism *Shewanella oneidensis* MR-1 (*S. oneidensis* MR-1).

Methods First, the mRNA expression data of *S. oneidensis* MR-1 under different oxygen levels were integrated into its PPI network to construct the active protein networks. Then, we studied the changes of key proteins and their interactions by comparative analysis of multiple pairs of active networks.

Results The analysis of node centrality and its changes in the active networks under high and low oxygen levels shows that most of the key nodes in the network are ribosomes or proteins closely related to ribosomes. The results of our centrality versus centrality change analysis of nodes show that the two proteins FlgB and PetA are the largest changed proteins. Among these proteins, the FlgB protein is the structural component of flagella, while PetA protein is closely related to cytochrome *c*. Furthermore, we also analyzed the changes in protein–protein interactions in the active networks under different oxygen levels, identified the key interactions in each pair of active networks, and finally screened out the key interaction Tig-RplX that exists in three pairs of active networks.

Conclusion Our results indicate that the translational processes of proteins and the corresponding translation efficiency may play an important role before and after the activation of the EET process of *S. oneidensis* MR-1. Furthermore, this study can also provide some guidance for identifying key proteins and interactions under different conditions for this species.

Keywords Network comparison, Key proteins, Key interactions, Extracellular electron transfer

Introduction

Extracellular respiration refers to the process in which electroactive microorganisms transfer electrons produced in their metabolism to the outside of the cell under anaerobic conditions, reduce extracellular electron receptors, and produce energy to maintain their own growth. Such extracellular electron transfer (EET)

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process is generally believed to have an important impact on the cycling of carbon, nitrogen, sulfur, iron, manganese and other elements in the Earth's environment (Jiang et al. 2019). At present, this characteristic of electroactive microorganisms also makes them an important research object in bioelectrochemical systems, which have a wide range of applications in energy production, wastewater treatment, bioremediation and chemical synthesis (Logan et al. 2019; Lovley and Holmes 2022).

In recent years, with the rapid development of high-throughput sequencing technology and bioinformatics methods, an increasing number of scholars have begun to explore the EET process of electroactive microorganisms through various "omics" technologies and "network" methods. Huang (2018) analyzed the transcriptome data of *S. oneidensis* MR-1 in different culture environments and found that the expression of genes related with iron reduction metabolic pathways were increased in iron and sulfur environments. They concluded that an iron-sulfur environment can improve the efficiency of EET. Grobbler et al. (2018) used quantitative proteomics to analyze cell changes and found that the abundance of *S. oneidensis* MR-1 electron transfer proteins varied with electrode potential. Yang (2020) combined metagenomics, single-cell genomics and metaproteomics, and found that the basal metabolism of biofilms remained active at low temperatures, but oxidative metabolism was inhibited under suboptimal conditions and affected the EET rate. Alves et al. (2015) analyzed the interaction network of various cytochromes and found that the microtetraploid cytochrome STC played a central role in the anaerobic respiratory metabolism of *S. oneidensis* MR-1 and was helpful in maintaining the periplasmic redox network of multifunctional anaerobic metabolism of *S. oneidensis* MR-1. Ding and Sun (2018) also identified the key active proteins of the *S. oneidensis* MR-1 EET process based on network analysis method and found a variety of *c*-type cytochromes and signal processing proteins that played a key role in the EET process.

These studies explore the EET process mainly through omics data and interaction networks. The analysis of omics data usually compares the changes in mRNA/protein expression under different conditions. The studies of biological networks mainly focus on the networks under certain conditions but fail to make further comparative analysis of the differences between these networks. Zheng et al. (2016) combined gene expression and protein–protein interactions to construct a coexpressed protein interaction network (CePIN) to study coronary heart disease, and the results showed that the comparative analysis between CePINs was helpful to further study the dynamic changes in disease-related biological processes in different states. Therefore, the effects of different oxygen conditions on the electrogenic bacterium *S. oneidensis* MR-1 EET process were investigated by comparative analysis of the protein networks in this study. First, we integrated the PPI network of *S. oneidensis* MR-1 and its mRNA expression level data under different oxygen levels to obtain three pairs (high O_2 vs low O_2) of active protein networks (active networks). Then, we analyzed the centrality of nodes in each pair of active networks and the change of centrality, obtained the key proteins of each pair of active networks under different oxygen levels. Finally, we compared the changes in the interactions between each pair of active networks and analyzed the key interactions. Taking together, our results indicate that the translational processes of proteins and the corresponding translation efficiency may play an important role before and after the activation of the EET process of *S. oneidensis* MR-1. Furthermore, this study can also provide some guidance for identifying the key proteins and interactions under different conditions for this species.

Materials and methods

Construction of the active network

Changes in oxygen levels can lead to differences in protein expression and changes in protein–protein interactions before (i.e., high oxygen level) and after (i.e., low oxygen level) activation of EET. We first obtained the mRNA expression data of *S. oneidensis* MR-1 at different oxygen levels from Taylor et al. (2013), where the experiments are divided into three pairs according to the oxygen level (20% high oxygen vs 8.5% low oxygen): S1 vs S4, S2 vs S5 and S3 vs S6. Then, we downloaded the interaction information data between all proteins of *S. oneidensis* MR-1 from the STRING database (http://string-db.org/) (Szklarczyk et al. 2019). The filter was performed according to the following guidelines: (1) the total confidence score is greater than or equal to 0.6; (2) the direct experimental score is greater than 0. Finally, we integrated the above mRNA and protein network data of *S. oneidensis* MR-1 and used the PathExt method proposed by Sambaturu et al. (2021). The highly active paths in the protein network were identified by network weighting, and then these active paths were extracted to construct the active protein network (active network).

Identification of key proteins based on node centrality

The centrality index of a node generally refers to a function $C(V_i)$ that assigns a certain value to each node in the network. There are many different definitions and formulas that can be used to measure the centrality of a node in the network.

We used the NetworkX package (Hagberg et al. 2008) to calculate the degree centrality, betweenness centrality, closeness centrality and eigenvector centrality of each

active network. Then, to integrate these multiple indicators, we used the formula (1) to calculate the standard centrality score (SCS_v) of each node.

$$SCS_v = \frac{1}{k}\sum_{k}\left(CS_v/CS_{\max}\right)_k \quad (1)$$

where CS_v is the centrality score of node V in a certain centrality metric method, and CS_{max} is the maximum value of all node centrality values in the corresponding centrality metric method.

Identification of key proteins based on node centrality changes

In order to identify the proteins with large changes under different oxygen levels, we further calculated the difference values of the change in centrality measure of the proteins in each pair of active networks, sorted the resulting difference values from large to small, and took the top 20 proteins with the largest changes as the key proteins based on the changes in centrality in each pair of active networks. In addition, we screened out the key proteins that were simultaneously present in the three pairs of active networks.

Identification of key protein–protein interactions

To analyze the changes in protein–protein interactions under different oxygen levels, we used the Volta package (Pavel et al. 2021) to compare all the interactions in each pair of active networks, identified the emerging interactions after the activation of the EET process, and selected the emerging interactions as candidate key protein–protein interactions.

Visual analysis

The PPI network can intuitively reflect the interactions between proteins, and the visualization of the active networks and their changes is completed mainly by NetworkX package (Hagberg et al. 2008). To better reflect the changes in protein–protein interactions between the three pairs of active networks under different oxygen levels, we drew a Sankey diagram (https://echarts.apache.org/examples/zh/#chart-type-sankey). In addition, the Venn diagram was constructed through an online website (http://bioinformatics.psb.ugent.be/webtools/Venn/).

Results and discussion

Construction and structural analysis of the active network

An active biological network refers to a subnetwork from a complete network in which proteins are expressed at a high level. Active biological networks can be used to identify proteins that are significantly differentially expressed in a biological process and their interactions (Sun et al. 2020). Therefore, we constructed and comparative analyzed the active networks of *S. oneidensis* MR-1 under different oxygen levels in this study. As described in the Materials and methods section, we integrated the mRNA expression level data of *S. oneidensis* MR-1 under different oxygen levels with the PPI network to construct active protein networks: S1Net, S2Net, S3Net, S4Net, S5Net, and S6Net.

Because the change in oxygen level will significantly affect the EET process of electrogenic microorganisms, according to the original experimental data (i.e., S1 and S4, S2 and S5, and S3 and S6), the six active networks are grouped into three pairs according to their different oxygen levels; that is, S1Net and S4Net, S2Net and S5Net, S3Net and S6Net. Here, the first three networks (i.e., S1Net, S2Net, S3Net) are active networks at high oxygen levels (i.e., the EET process inactivation state), and the last three networks (i.e., S4Net, S5Net, S6Net) are active networks at their corresponding EET process activation state at low oxygen levels.

We first calculated the basic network information indicators of these six active networks (Table 1). From the basic information indicators of these networks (especially the degree value heterogeneity and the average shortest path length), S1Net, S2Net, and S3Net are close, while the basic network information indicators of S4Net, S5Net, and S6Net are close. This result is highly consistent with the experimental conditions underlying

Table 1 Basic network information indicators of the six active networks

Name	Nodes	Edges	Diameter	Average degree	Average clustering	Density	Degree heterogeneity	Average shortest path length
S1Net	215	552	12	2.57	0.24	0.02	2.64	3.78
S2Net	187	343	10	1.83	0.26	0.02	2.37	3.70
S3Net	183	324	10	1.77	0.29	0.02	2.31	3.78
S4Net	190	247	13	1.30	0.15	0.01	2.15	4.08
S5Net	169	229	13	1.36	0.25	0.02	2.09	4.04
S6Net	169	234	13	1.38	0.25	0.02	2.12	3.90

these active networks: S1Net, S2Net, and S3Net are data at high oxygen levels, while S4Net, S5Net, and S6Net are data at low oxygen levels, further supporting that active biological networks can be used to identify genes that are significantly differentially expressed in certain biological processes and their interactions.

At the same time, microorganisms must respond appropriately to changing environmental conditions (Erez et al. 2020; Moreno-Gámez et al. 2020). Therefore, the changes in these active networks should also be helpful to understand the changes in the environment, that is, the importance and changes in proteins and their interactions in the network before and after the activation of the EET process.

We further compared several active networks under the same conditions. As shown in Fig. 1, there are 172 common proteins in the three active networks (S1Net, S2Net, and S3Net) at high oxygen levels and 153 common proteins in the three active networks (S4Net, S5Net, and S6Net) at low oxygen levels, with fewer differential proteins overall for the active networks in both cases, showing that under the same experimental conditions, microorganisms tend to use similar proteins to respond to the environment (Padi and Quackenbush 2018). However, the interactions between these proteins are quite different (Fig. 2), suggesting that the interactions between biomolecules are highly variable. Furthermore, we also calculated the ratios between changed and unchanged proteins in each pair of active networks (0.38, 0.27, 0.35) and between changed and unchanged interactions (1.77, 0.69, 0.57). These results also show that the degree of change of interaction in biological networks is higher than the degree of change of proteins themselves under different experimental conditions.

Node-based key protein identification

First, we identified key proteins through the centrality analysis of nodes. The centrality of a node can measure its relative importance in the network, and researchers have proposed a variety of centrality metrics: the

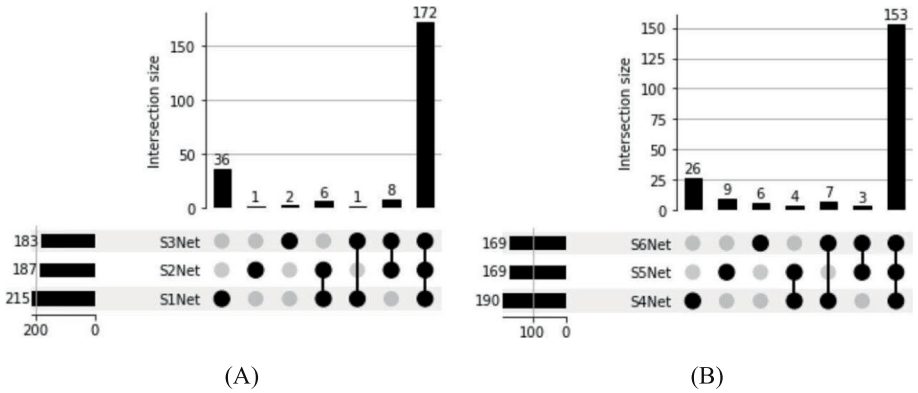

Fig. 1 Comparison of protein information among different active networks. Note: **A** Three active networks S1Net, S2Net and S3Net in the inactive state of EET. **B** Three active networks S4Net, S5Net and S6Net in the activated state of EET

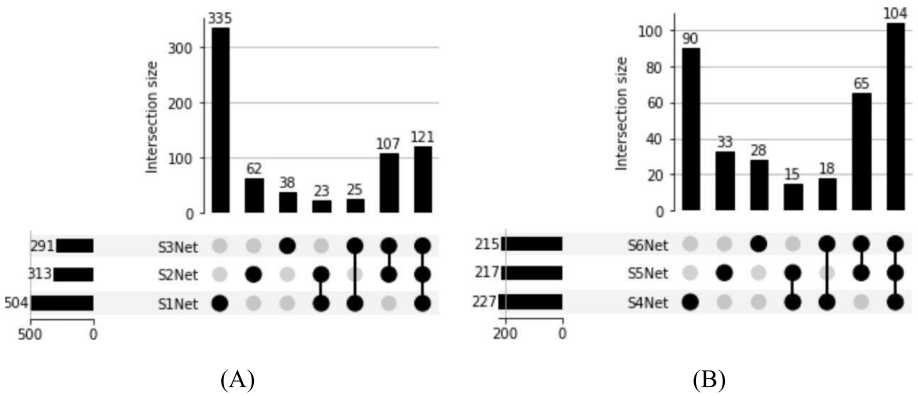

Fig. 2 Comparison of interaction information among different active networks. Note: **A** Three active networks S1Net, S2Net and S3Net in the inactive state of EET. **B** Three active networks S4Net, S5Net and S6Net in the activated state of EET

number of nodes connected to a node in the network is the degree centrality; the reciprocal of the distance from a node to all other nodes in the network is the closeness centrality; the number of times a node in the network is passed by the shortest path is the betweenness centrality etc. (Li et al. 2020).

Studies have shown that the combined use of several centrality methods is usually more effective (Gong 2020). Therefore, we used the methods of degree centrality, closeness centrality, betweenness centrality and eigenvector centrality, and used a standard centrality score to comprehensively use these centrality analysis methods. To identify the proteins that are always in the key position under different oxygen levels, we extracted the proteins that coexist in each pair of active networks and the interactions related to these proteins, calculated the standard centrality score of all nodes in each pair of active networks, and then calculated the average score of each node in each pair of active networks. Finally, according to the average score of each node, the top 20 key proteins that are always in key positions in each pair of active networks are determined.

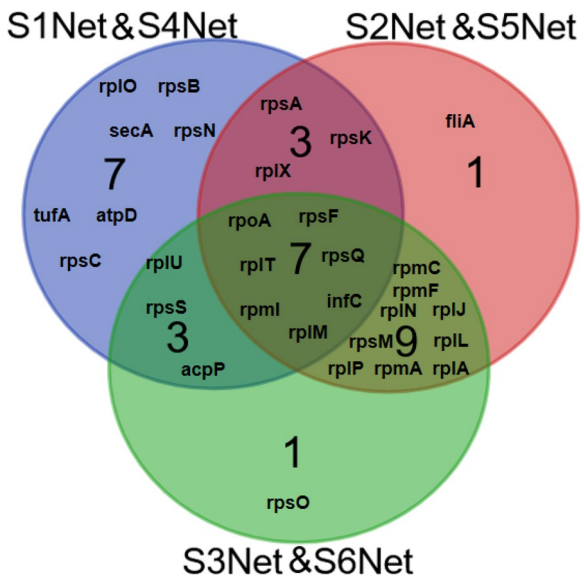

Fig. 3 Relationship of proteins identified by node centrality for three pairs of active networks

We compared the top 20 key proteins of these three pairs of active networks (Fig. 3) and found that they have seven common proteins: InfC, RplT, RpmI, RplM, RpsF, RpsQ, and RpoA. Changes in expression level further support the importance of these proteins, as five of these seven proteins increase the expression level, and the other two maintain (at least not significantly decrease) the expression level (Table 2). Functional analysis of these proteins shows that except for the DNA-directed RNA polymerase subunit RpoA, which is related to RNA synthesis, the other six proteins are ribosomal proteins or proteins related to ribosomal proteins; that is, these six proteins are all related to protein translation.

Subsequently, to study the changes in key nodes in the network under different oxygen levels (i.e., before and after the activation of the EET process), we identified the key proteins according to the changes in node centrality in each pair of active networks. Specifically, for the two active networks S1Net and S4Net, we first excluded the proteins they independently own and then identified the top 20 key proteins with the largest changes in nodes according to the difference in centrality measures of each node in the network. Supplementary Table S1 gives the identifications (IDs) of these proteins, and their names, the centrality measure of S1Net, the centrality measure of S4Net, the difference in the centrality measures of this pair of active networks, and also the functions of them. According to the information in Supplementary Table S1, the key 20 proteins identified are also mainly ribosomal proteins, which are related to the translation process.

In addition to the translation process proteins, we also screened out the PetA protein related to cytochrome from these 20 key proteins (blue part of Fig. 4). PetA is a component of the ubiquitin cytochrome *c* reductase complex, which can generate an electrochemical potential coupled with ATP synthesis. Previous studies have shown that CymA plays a crucial role in the electron

Table 2 The expression levels of the seven common proteins in Fig. 3

Name	S1Net	S4Net	S4:S1	S2Net	S5Net	S5:S2	S3Net	S6Net	S6:S3
InfC	23.59	107.69	**4.57**	30.42	69.07	**2.27**	37.10	85.76	**2.31**
RplT	11.44	49.57	**4.33**	34.70	140.75	**4.06**	37.54	132.44	**3.53**
RpmI	21.38	85.98	**4.02**	49.01	178.68	**3.65**	49.39	168.11	**3.40**
RplM	1.49	4.39	**2.95**	5.61	10.40	**1.85**	4.66	13.52	**2.90**
RpsF	4.29	7.44	**1.73**	5.47	9.36	**1.71**	3.86	9.37	**2.43**
RpsQ	10.68	14.37	1.35	23.96	17.47	0.73	24.40	24.10	0.99
RpoA	9.14	9.45	1.03	10.94	10.17	0.93	9.10	8.64	0.95

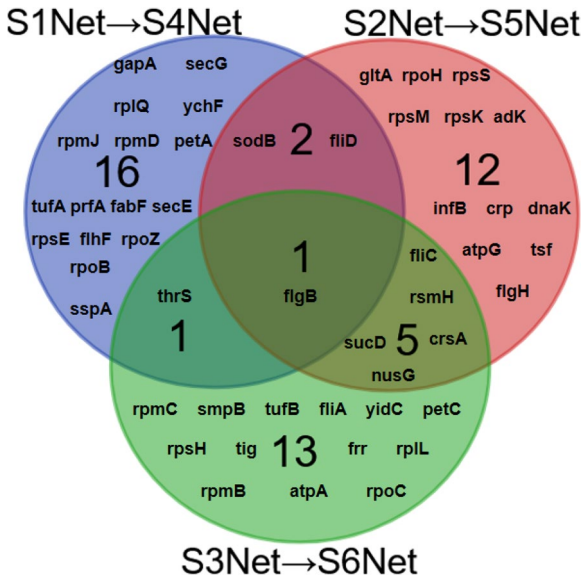

Fig. 4 Relationship of genes identified by node centrality changes for three pairs of active networks

transport process of *S. oneidensis* MR-1 (Schwalb et al. 2003; Yin et al. 2015), while the *petABC* operon is proposed to encode a functional substituent of CymA in *Shewanella* genome (Fu et al. 2014). Therefore, PetA protein may also play an important role in the EET process.

Similarly, we also obtained the top 20 key proteins with the largest difference in centrality metrics in the other two pairs of active networks (i.e., S2Net and S5Net, S3Net and S6Net) (Supplementary Tables S2 and S3), and the obtained key proteins functionally acted similarly to the S1Net and S4Net group experiments. Therefore, most of the key proteins, which are identified based on node centrality or based on changes in node centrality, are related to the process of protein translation. Recent studies have shown that translation efficiency is a major determinant in the regulation of gene expression levels in *S. oneidensis* MR-1 (Ding and Sun 2022). These results not only further support the above conclusion but also imply that there are great changes in the protein translation process before and after the activation of the EET process, and the proteins closely related to the protein translation process identified by us may play an important role before and after the activation of the EET process.

In addition, we further analyzed the key proteins identified based on node centrality changes and screened out the common key protein FlgB in three pairs of active networks (Fig. 4). Because each pair of active networks has a high oxygen level vs a low oxygen level and the change in oxygen level has a significant impact on the EET process, we speculated that the most important FlgB protein might play a role in EET process. Here, FlgB is part of the structural component of the flagellum and bacterial movement device.

On the one hand, the FlgB protein is in a more important position when the oxygen level is reduced, indicating that FlgB is more active and expressed at a higher level under oxygen-deficient conditions than under oxygen-sufficient conditions, possibly because, under the condition of sufficient oxygen, most of the electron acceptors are oxygen, and the expression level of flagella is low. In the absence of oxygen, the electron acceptor is outside the cell, and the electrons produced must pass through the electron carrier to be transmitted to the outside of the cell, which may require movement through the flagellum (Ma et al. 2011).

On the other hand, in the *Geobacter sulfurreducens* strain, flagella can promote the formation of biofilms and act as a biofilm matrix scaffold to promote the ordered arrangement of cytochromes in the biofilm matrix to accommodate more extracellular cytochromes and increase the electron diffusion rate in the biofilm (Liu et al. 2019). In other words, the increase in flagellar expression is positively correlated with biofilm thickness and the outer membrane *c*-type cytochrome in the anodic biofilm matrix (Liu et al. 2019), and cytochrome *c* plays a very important role in the EET process. Therefore, flagella are also closely related to the EET process of cells. Taken together, the FlgB protein should also play an important role in EET.

Edge-based protein interaction analysis

To identify important interactions under different oxygen levels, we compared the changes in interactions in three pairs of active networks. Figure 5A shows the change from S1Net to S4Net, it is clear that the most critical protein under different oxygen levels (i.e., deactivated or activated EET process) is SO_2302 (RplT), which further reflects the above results of the key proteins identified based on node centrality. This result indicates that SO_2302 (RplT) is not only a key protein in the network but also plays a significant role by interacting with other proteins.

During the change from S1Net to S4Net, 310 pairs of interactions disappeared, and 33 pairs of interactions were added (Fig. 5B); that is, more interactions disappeared than new interactions after the activation of the EET process. In response to changes in environmental conditions, microorganisms need to synthesize new proteins or generate new interactions, and the synthesis of new proteins or the generation of new interactions requires sufficient synthetic precursor proteins (Balakrishnan et al. 2021). However, precursors are limited, so in response to changes in environmental conditions, the lack of precursors may lead to the inability to

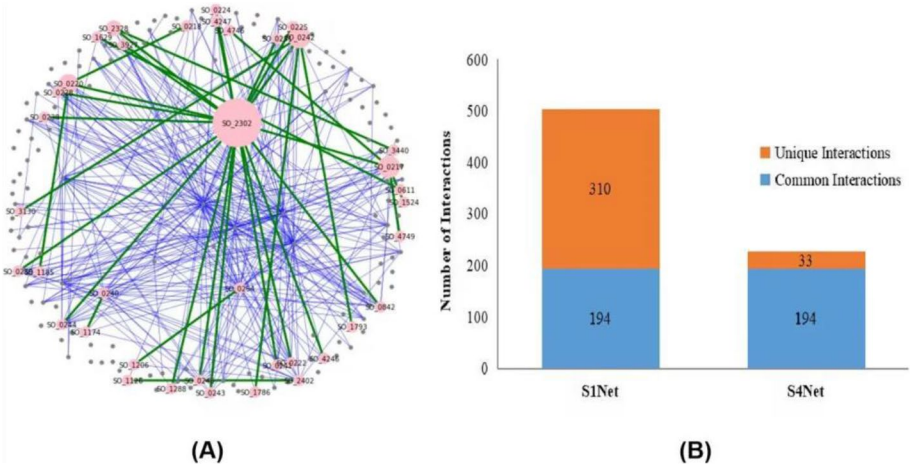

Fig. 5 Changes in interaction in active networks. Notes: **A** Interaction of S1Net and S4Net. The blue edges in the figure represent the protein–protein interactions that disappeared in the process from S1Net to S4Net, the green edges represent the protein–protein interactions that are newly added in the process from S1net to S4net, and the common protein–protein interactions between S1Net and S4Net are not shown in the figure. The pink nodes are the nodes related to the newly added edges. The size of the node is determined by the degree value of the node. **B** Veen plot of interaction data in S1Net and S4Net

synthesize enough proteins, resulting in far more lost interactions than new ones. At the same time, these new interactions are generally necessary to respond to changes in environmental conditions; that is, the new interactions can be regarded as the key protein–protein interactions before and after the activation of EET process. The analysis of the interaction changes in the two pairs of active networks, S2Net and S5Net, S3Net and S6Net, also identified the key protein–protein interactions before and after the activation of the EET process under corresponding conditions.

We further compared the changes in protein–protein interactions of all three pairs of active networks (Fig. 6). The results showed that there were fewer common interactions (Common123) between the three networks (S1Net, S2Net, S3Net) at high oxygen levels and fewer common interactions (Common456) between the three networks (S4Net, S5Net, S6Net) at low oxygen levels, possibly because the interactions between proteins

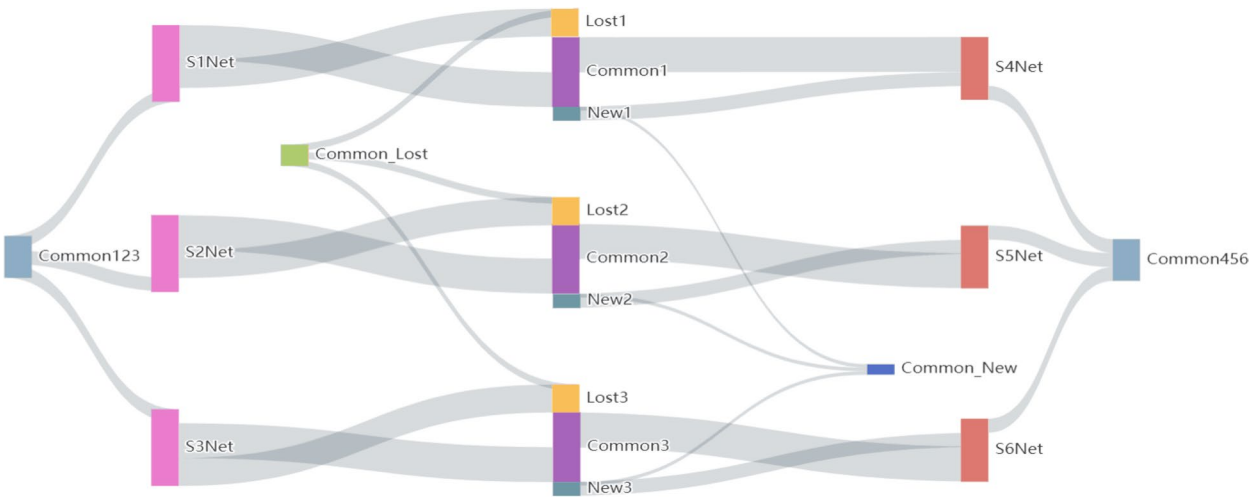

Fig. 6 Differences in the interaction among three pairs of active networks. Note: Common123 presents the same interactions at high oxygen levels in the experiment, Common456 presents the same interactions at low oxygen levels in the experiment, Common_Lost presents the same interactions in which three pairs of active networks disappear together, and Common_New presents the same interactions in which three pairs of active networks add together. In S1Net and S4Net, Common1 represents common interactions, Lost1 presents interactions that disappear after the change in experimental conditions, and New1 presents interactions that are newly added after the change in experimental conditions

are highly complicated, as the main pattern of proteome organization in the cell and the context of PPIs are intensely dependent on cellular states (Ciuffa et al. 2022). In other words, under the same experimental conditions, although it is generally believed that the expressed proteins will be highly consistent, we found that the interactions among these proteins were largely different.

Similarly, in the process of changing oxygen conditions, even if the experimental conditions are the same, the common lost interaction (Common_Lost) and the common new interaction (Common_New) in the three groups of experiments are also few. In addition, we also found that the three pairs of active networks have more interactions that remain unchanged after the change in oxygen conditions, which may be the interactions that cells retain to maintain minimum survival (Honda et al. 2022).

On the other hand, the key protein–protein interactions that exist simultaneously in the multi-pair active networks should be very important in the whole process of environmental changes. Therefore, we further analyzed the key protein–protein interactions screened from the changes in protein–protein interactions in the three pairs of active networks. As shown in Fig. 7, although the key protein–protein interactions identified in the three pairs of active networks are quite different, the Tig-RplX pair of interactions is a common key protein–protein interaction. Therefore, the protein–protein interaction of Tig-RplX may play an important role under changed oxygen levels.

Here, the Tig protein is involved in protein export, and the Tig protein plays a chaperone role by maintaining the newly synthesized protein in an open conformation. RplX is one of two assembly initiator proteins binding directly to the 5′-end of 23S rRNA, where it nucleates assembly of the 50S subunit, both of which are related to protein synthesis. Therefore, following the changed oxygen levels, the great changes in translation-related proteins were not only reflected in the addition and loss of proteins but also in the interaction between common translation proteins in the network. After the change in environmental conditions, Tig-RplX gradually occupied the dominant position, indicating that the interaction between Tig-RplX played a huge role in the process of protein synthesis.

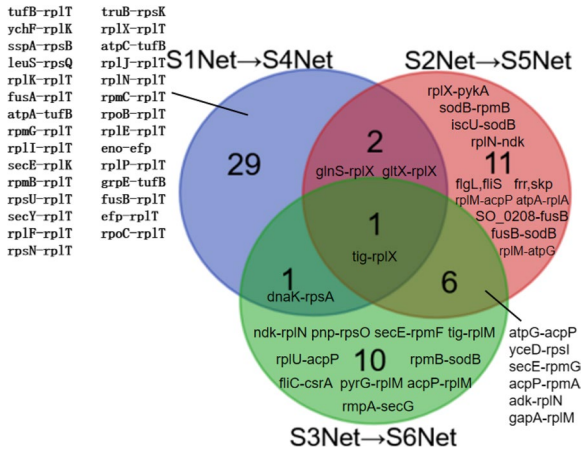

Fig. 7 Venn diagram of new key interactions in the three pairs of active networks

Conclusion

In this study, we integrated the mRNA expression data of *S. oneidensis* MR-1 under different oxygen levels to construct the active protein networks of the bacterium, and studied the specific changes under these conditions by comparing pairs of active networks. We first compared the centrality and centrality changes of proteins in each pair of active networks and found that most of the key proteins were ribosomes or proteins that were closely related to ribosomes, indicating that protein translation played an important role before and after the activation of the EET process. Furthermore, we found that both FlgB and PetA proteins varied greatly in each pair of active networks. Combined with the relevant literature, we speculated that both FlgB and PetA played an important role in EET. We also compared the protein–protein interactions of each pair of active networks and screened the key interaction Tig-RplX that exists in multiple pairs of active networks, indicating that this pair of interactions should be closely related to the changed oxygen levels. Nevertheless, due to the transcriptome level and proteome level are not completely consistent, and the existence of a specific mRNA does not mean that it will be effectively translated into a functional protein under a real cellular environment, the identified key proteins and key protein interactions need to be further confirmed at the proteome level as well as experimental investigation.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13213-023-01718-7.

Additional file 1: Supplementary Table S1. Genes screened according to the difference of centrality measurement in S1Net and S4Net. **Supplementary Table S2.** Genes screened according to the difference of centrality measurement in S2Net and S5Net. **Supplementary Table S3.** Genes screened according to the difference of centrality measurement in S3Net and S6Net.

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Authors' contributions
Xiong CW: conceptualization, methodology, writing—original draft. Tong H, Ding DW: methodology, data analysis, and writing—review and editing. He XQ: conceptualization, funding acquisition, and writing—review and editing. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated and analyzed during this study are included in this article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflicts of interest.

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