Determining the Significance of the MICOS Protein Complex on the Frequency of Spontaneous Cellular Respiration Loss in *Saccharomyces cerevisiae*

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Abstract

The Mitochondria is a double-membraned organelle found in all eukaryotic cells. It is the organelle most known for taking nutrients from the cell, breaking it down, and turning it into energy; a process known as cellular respiration. The DNA of the mitochondria (mtDNA) is circular, and differs greatly from the nuclear genome. In order to prevent mutations, there are genes that present proteins involved in DNA repair mechanisms. Response to DNA damage, lack of nutrients and other stress conditions is an essential property of living systems. The coordinate response includes DNA damage repair, activation of alternate biochemical pathways, adjustment of cellular proliferation and cell cycle progression as well as drastic measures like cellular suicide which prevents proliferation of severely damaged cells (1). One gene complex, known as the MICOS Complex, is composed of six different genes. MICOS (Mitochondrial contact site and Cristae Organizing System) is a mitochondrial inner membrane complex that extends into the intermembrane space and has a role in the maintenance of crista junctions, inner membrane architecture, and formation of contact sites to the outer membrane (2). Mic60p can be described as the core component for the maintenance of the MICOS complex, controlling protein transport, mitochondrial DNA transcription, and the connection between the inner and outer mitochondrial membranes.

In the lab, a set of mutant strains, each representing one of the six genes from the MICOS complex have been developed. As one experiment, the *mic60Δ* mutant strain is compared to the wild type strain, *MIC60,* in an assay determining respiration loss, overall determining the significance of the MICOS complex on cellular respiration. Rich growth medias containing dextrose as the sole carbon source were used to determine spontaneous respiration loss in both the *mic60Δ* and *MIC60* strains initially. The *mic60Δ* strain has revealed a 2.05-fold increase in

loss of cellular respiration compared to that of the wild type when grown on dextrose. When these strains were grown on raffinose or fructose as the sole carbon source, the *mic60Δ* strain revealed a 1.46-fold increase in loss of cellular respiration compared to that of the wild-type. This data shows that Mic60p plays a vital role in the functioning mitochondria.

Introduction

Mitochondria

Mitochondria, the "powerhouses" of the cell, are double-membrane organelles that often form highly dynamic loose networks of tubules that frequently undergo fusion and fission, thereby continually changing the appearance of the network. Mitochondria communicate with the nucleus and are physically connected to other organelles by means of inter-organellar tethering. The highly contorted mitochondrial inner membrane is surrounded by the smooth outer membrane and has three domains: the inner boundary membrane that parallels the outer membrane; crista membranes, invaginations of the inner membrane that differ in shape depending on the cell type and physiological conditions; and crista junctions, narrow tubules that connect the inner boundary membrane with the cristae membrane. (3)

The mitochondria is essential for cellular respiration. The main function is to use carbohydrates to generate ATP through oxidative-phosphorylation. It is also involved in processes such as: calcium homeostasis, cell growth, cell death, and metabolism. The outer layer of the mitochondria is responsible for maintaining shape and structure all while controlling communication to other organelles. The inner membrane of the mitochondria has folds called cristae that increase surface area and is essential for mitochondrial function. The number of folds in a mitochondrial inner membrane differs depending on the energy demand for each cell. For

example, heart muscle cells can have two to three times more folds than other cells that may not require as much energy to function. Without these folds in the inner membrane, the mitochondria would not be able to keep up the energy demands of the organism. The cristae is embedded with proteins, including ATP synthase and a variety of cytochromes all aiding in cellular respiration, along with the electron transport chain. The electron transport chain creates an electrochemical gradient across the inner mitochondrial membrane. This gradient initiates the creation of ATP from ADP and inorganic phosphate. The mitochondria is not only essential for cellular respiration, it performs functions such as maintaining the proper concentration of calcium ions within the cell, and maintaining some hormones such as estrogen and testosterone.

Mitochondrial DNA

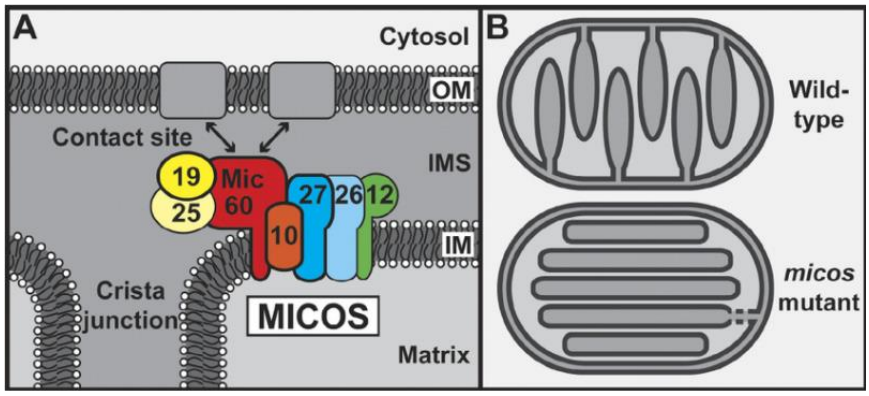
Mitochondrial DNA (mtDNA) is small, circular, found within the nucleus of eukaryotic cells, and contains thirty-seven genes. Mitochondrial DNA is unique because it is passed down maternally. The mtDNA of any person is almost identical to the mtDNA of the mother. The mitochondrial DNA is critically important for many of the pathways that produce energy within the mitochondria. And if there's a defect in some of those mitochondrial DNA bases, that is to say a mutation, there will be a mitochondrial disease, which will involve the inability to produce sufficient energy in things like the muscle and the brain, and the kidney (4). The size of the mtDNA in plant and fungi species varies greatly, some with as many as 11,300,000 base pairs. The mtDNA of humans is considerably smaller than that of plants and fungi, with a size of 11-28 bp compared to 19-1000 bp. Additionally, the mtDNA in humans does not contain introns, but the mtDNA in plants and fungi does. The replication process beings with priming, so DNA polymerase can use these primers as a foundation for replication. Mitochondrial DNA is also essential for ancestry tracing. Mitochondrial DNA is roughly ten times more susceptible to

mutations. Specific mutations can alter oxidative phosphorylation, resulting in an altered or diminished cellular respiration cycle.

MICOS Complex

The MICOS complex (Mitochondrial contact site and Cristae Organizing System), located on the inner membrane on the mitochondria, is a mitochondrial contact site and cristae organizing system. Recently, several groups identified a large protein complex, MICOS complex, that has a crucial role in the formation of cristae junctions, contact sites to the outer membrane, and the organization of inner membrane. In yeast, MICOS consists of at least six subunits: Mic60p, Mic10p, Mic19p, Mic26p, Mic12p and Mic27p (Figure 1). In mammals, five subunits of MICOS have already been identified, including Mic60p, Mic10p, Mic19p, Mic25p and Mic27p. However, the physiological functions of MICOS and how MICOS is assembled in mammals are largely unknown. Mic60p/Mitofilin, a key component of MICOS complex, was altered under several different pathological conditions. However, how the integrity of MICOS and the homeostasis of MICOS subunits are controlled and the physiological functions of MICOS complex in mammals still remain unknown. Even though cristae are found in all mitochondria capable of oxidative phosphorylation, only Mic10p and Mic60p appear to be conserved throughout eukaryotes. The remaining 4 or 5 known MICOS subunits are specific to the supergroup Opisthokonta, which includes yeast and mammals that are the only organisms in which this complex has been analyzed experimentally (5).

Figure 1: MICOS Complex(10)



A: MICOS complex necessary for functioning mitochondria with contact sites between inner and outer membranes. In yeast, there are six subunits that have been identified. B: Shape of the wild-type of the mitochondrial inner membrane with cristae junctions and cristae. *Micos* mutant mitochondria show cristae membranes detached from the inner membrane and form stacks in the inner membrane.

Mic60p

In the present study, we show that the stability of Mic60p/Mitofilin is dependent on its assembly into MICOS complex by direct interaction with Mic19p/CHCHD3. Moreover, we reveal that the integrity of MICOS complex is critical for the maintenance of mitochondrial morphology and the organization of mtDNA nucleoids (6). Mic60p, also known as Mitofilin, HMP or Fcj1, is a mitochondrial inner membrane protein first identified in the heart. As a crucial component of the mitochondrial contact site and cristae organizing system (MICOS), Mic60p has been well characterized in controlling mitochondrial morphology. Mic60p plays important roles in many aspects of mitochondrial functions. Suppression of Mic60p increases mitochondrial membrane potential and the production of reactive oxidative species. We previously reported that Mic60p also regulates cytochrome c release during apoptosis. Recently, we found that Mic60p is involved in the development of cardiomyopathy and that *Mic60p* overexpression promotes cardiac hypertrophy in response to hypertrophic stimuli. Mic60p is also involved in import of intermembrane space (IMS) proteins, probably by positioning Mia40p relative to the TOM complex to receive incoming proteins; ortholog of mammalian Mitofilin (7). However, the physiological behavior of Mic60p and the mechanism how Mic60p functions

remain incompletely understood (8). However, additional research on Mic60 has been conducted to determine its role in the progression of neuromuscular diseases such as Parkinson's disease. The mitochondrial structural protein Mic60, also known as mitofilin, is critical for maintaining mitochondrial architecture and function. Loss of Mic60 is associated with detrimental effects on mitochondrial homeostasis. Growing evidence now implicates Mic60 in the pathogenesis of PD (9).

Research Aims

This study aims to find the impact of the function Mic60p on the mitochondrial membrane and its effects on cellular respiration. In order to test the role of Mic60p on mitochondrial function, an assay determining respiration loss is performed. Results show a loss of respiration in the *mic60Δ* strain, revealing the importance of Mic60p in mitochondrial functioning. Using different sugars to provide alternatives for carbon sources should alter the rates of cellular respiration in the yeast. Yeast uses sugar during fermentation to turn monosaccharides into carbon dioxide and ethanol. Sugars such as glucose and sucrose provide high yields of carbon dioxide, while sugars such as fructose produce much lower yields.

Experimental Procedures

Table 1. Strain Names and Genotypes

MIC60 (DFS188)	MATa ura3-52 leu2-3, 112ly2 his3 arg8::hisG
mic60Δ	MATa mic60Δ::KAN ura3-52 leu2-3, 112ly2 his3 arg8::hisG

Plate Preparation- YPG

YPG plates contain 20% glycerol; a nonfermentable carbon source. To prepare these plates, 10 grams yeast extract, 20 grams bacto peptone, 25 grams agar, 900ml dH_2O, and a stir bar were measured and mixed into a 2000mL flask. The flask was then placed in an autoclave and set to the liquid 30 cycle to sterilize all components. After autoclaving, 100mL of 20% glycerol was mixed. Once cooled, the liquid from the flask was poured into 30 empty petri dishes and left out to cool overnight. The following day, the plates were placed back into the petri dish wrapped in groups of 15 and stored in the cool room for future use.

Plate Preparation- YPD

YPD plates contain dextrose, a fermentable carbon source. To prepare these pates, 10 grams yeast extract, 20 grams bacto peptone, 25 grams agar, 1000mL dH_2O, 20 grams dextrose and a stir bar were measured and mixed into a 2000mL flask. The flask was then placed in an autoclave and set to the liquid 30 cycle to sterilize all components. Once cooled, the liquid from the flask was poured into 30 empty petri dishes and left out to cool overnight. The following day, the plates were placed back into the petri dish wrapping in groups of 15 and stored in the cool room for future use.

Plate Preparation- YPG+ 0.2% Dextrose

YPG + 0.2% dextrose plates contain dextrose as the sole carbon source. To prepare these plates, 10 grams yeast extract, 20 grams bacto peptone, 25 grams agar, 2 grams dextrose, 900mL dH_2O, and a stir bar were measured and mixed into a 2000mL flask. The flask was then placed in an autoclave and set to the liquid 30 cycle to sterilize all components. After autoclaving, 100mL of 20% glycerol was mixed. Once cooled, the liquid from the flask was poured into 30 empty

petri dishes and left out to cool overnight. The following day, the plates were placed back into the petri dish wrapping in groups of 15 and stored in the cold room for future use.

Plate Preparation- Raffinose

These plates contain raffinose as the sole carbon source. To prepare these plates, 10 grams yeast extract, 20 grams bacto peptone, 25 grams agar, 1000mL dH_2O, 20 grams raffinose, and a stir bar were measured and mixed into a 2000mL flask. The flask was then placed in an autoclave and set to the liquid 30 cycle to sterilize all components. Once cooled, the liquid from the flask was poured into 30 empty petri dishes and left out to cool overnight. The following day, the plates were placed back into the petri dish wrapping in groups of 15 and stored in the cool room for future use.

Plate Preparation- Fructose

These plates contain fructose as the sole carbon source. To prepare these plates, 10 grams yeast extract, 20 grams bacto peptone, 25 grams agar, 1000mL dH_2O, 20 grams fructose, and a stir bar were measured and mixed into a 2000mL flask. The flask was then placed in an autoclave and set to the liquid 30 cycle to sterilize all components. Once cooled, the liquid from the flask was poured into 30 empty petri dishes and left out to cool overnight. The following day, the plates were placed back into the petri dish wrapping in groups of 15 and stored in the cool room for future use. Media Components are as follows:

Table 2. Media Components

YPG	YPG + 0.2 % Dextrose	YPFruc
Stir Bar	Stir Bar	Stir Bar
Yeast Extract 10g	Yeast Extract 10g	Yeast Extract 10g
Bacto Peptone 20g	Bacto Peptone 20g	Bacto Peptone 20g
Agar 25g	Agar 25g	Agar 25g
dH_2O 900mL	dH_2O 900mL	dH_2O 1000mL
20% Glycerin 100mL	20% Glycerin 100mL	Fructose 20g
	Dextrose 2g	

YPD	YPRaf
Stir Bar	Stir Bar
Yeast Extract 10g	Yeast Extract 10g
Bacto Peptone 20g	Bacto Peptone 20g
Agar 25g	Agar 25g
dH_2O 1000mL	dH_2O 1000mL
Dextrose 20g	Raffinose 20g

Patching

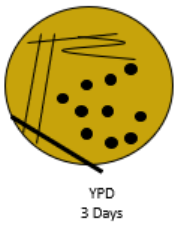
The yeast strain to be tested was removed from the -70°. Using a sterile pipette, a small portion of the frozen sample is placed on the appropriate growth medium. With a sterile wooden toothpick, the sample is spread in a circular motion on the plate, creating a patch of the given sample as seen in Figure 2. The plates are then stored in the warm room at 30°C for use the following day.

Figure 2: Patching on YPG

Streaking

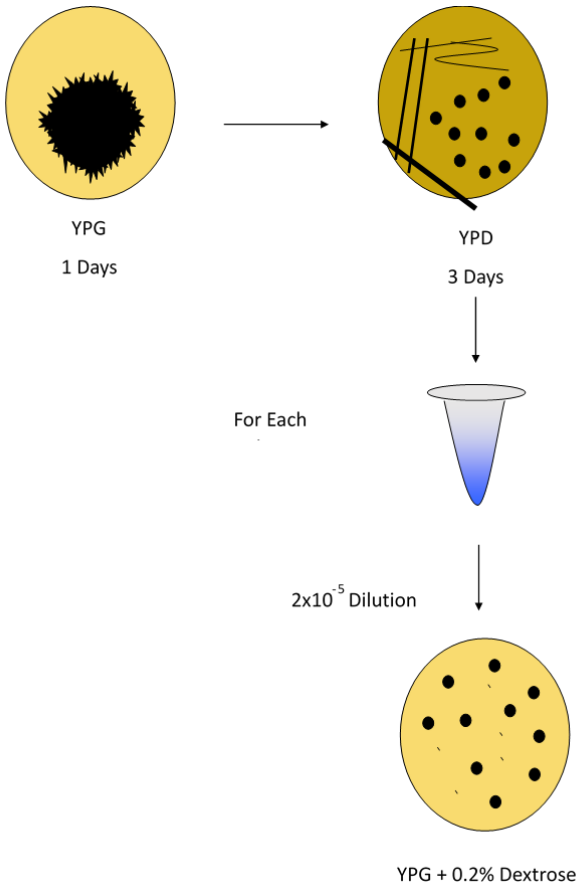
From the patch of cells, use a sterile wooden toothpick to transfer a small sample of the patch to one side of a plate with the appropriate growth medium. Using the other side of the toothpick, diagonal lines from the original streak to the other side of the plate are made to create future colonies on the plate. The streaking process is displayed by Figure 3. This is repeated into three growth plates to ensure enough colonies have grown for use in the assay. These plates are then incubated in the warm room at 30°C for one day prior to use.

Figure 3: Streaking



Respiration Loss Assay

Figure 4: Respiration loss assay



The respiration loss assay is depicted in Figure 4 above. The yeast strain to be tested was first patched onto a YPG plate and incubated at 30°C for one day to ensure that the strain was fully respiration proficient prior to the assay. From the patch, cells were streaked for single colonies on YPD plates and allowed to grow at 30°C for 3 days prior to use. Cells growing on this plate do not need to be respiration proficient in order to grow. Fifteen colonies of a single test strain were individually placed into 15 microfuge tubes containing 100 ul of sterile water. Each tube was used to create a final dilution of 2 x 10^{-5} for the picked colony. 50ul of from each tube was pipetted onto a YPG + 0.2% dextrose plate that already contained 100ul of sterile

dH_2O. Using sterile glass beads, the mixture was spread on the entire surface of the plate. For the assay, a total of fifteen plates were used for an individual strain being tested. In order to determine the effect of a specific carbon source or sugar on respiration loss, the same process was used except that plates containing YPRaffinose or YPFructose was used in place of YPD in the assay.

Counting

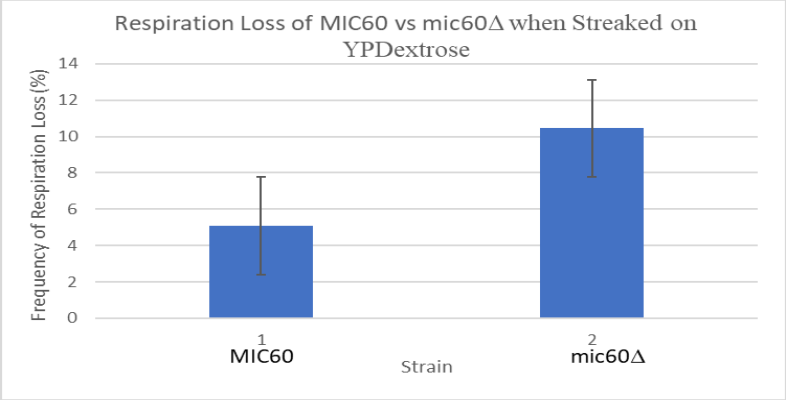
Two days after the assay, the plates are pulled from the warm room for counting. Using a hand-held counter and a sharpie. Each colony is accounted for the grew on each plate. After recording each plate and its colonies, plates are disposed of in a trash bag for removal. Respiration loss calculations are as follows: for each of the fifteen plates, the number of small colonies is divided over the number of total colonies, and multiplied by one-hundred. This calculates the percentage of small colonies relative to the number of total colonies grown. The median of these fifteen percentages is taken to determine a median respiration loss for each growth medium.

Results

The data show that *mic60Δ* plays a vital role in the functioning mitochondria, and that membrane binding of Mic60p is required for full mitochondrial activity. Using fifteen plates containing YPDextrose, an assay was done to achieve a $2.0x10^{-5}$ dilution of cells in water. Once pipetting the diluted solution to the plates with 50ul of the solution and 100ul of water, the plates were left in the warm room for two days before counting. After the two days, the large and small colonies that formed were counted to determine how dextrose affects the cells ability to repair themselves. This process was repeated over 5 weeks to determine an average respiration loss.

A respiration loss assay monitors the rate at which cells lose the ability to respire by quantitating petite *(rho-)* colony formation on media containing 2% glycerol and 0.2% dextrose. Glycerol is a non-fermentable carbon source. Cells must be able to respire and have an intact mitochondrial genome *(rho+)* in order to grow on media containing glycerol as the sole carbon source. Dextrose is a fermentable carbon source. If cells are lacking an intact mitochondrial genome *(rho-)* and therefore fail to respire, they can use the anaerobic metabolic pathway called fermentation to produce ATP and remain viable.

Figure 5: Effect of YPDextrose on Respiration Loss



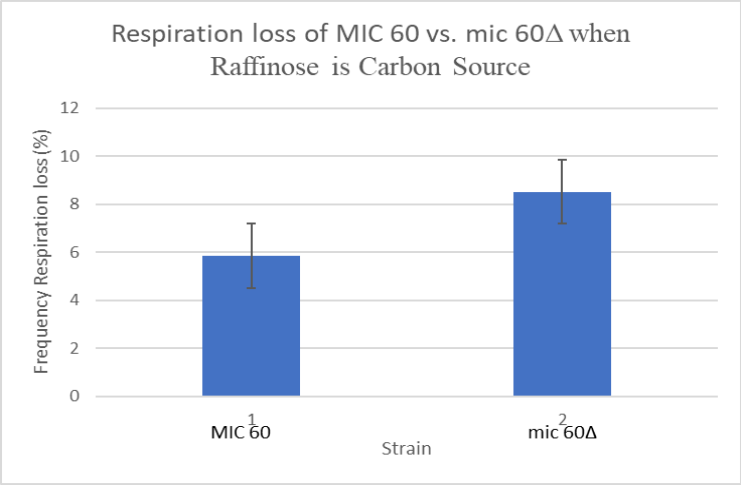
MIC60 and *mic60Δ* strains were used in a respiration loss assay. The average frequency of respiration loss for the two strains are shown in Figure 5 and Table 3. The median for spontaneous respiration loss in the *MIC60* wild-type was 5.084695%. The median for spontaneous respiration loss in *mic 60Δ* mutant strain was 10.4435%. The mutant strain demonstrated a 2.05-fold increase to 10.44% in spontaneous respiration loss compared to the 5.08% observed in the wild type strain. Cells must be able to respire and have an intact mitochondrial genome *(rho+)* in order to grow on media containing glycerol as the sole carbon source. Dextrose is a fermentable carbon source. If cells are lacking an intact mitochondrial

genome *(rho-)* and therefore fail to respire, they can use the anaerobic metabolic pathway called fermentation to produce ATP and remain viable.

Using the same dilution process as mentioned above, the solution was then plated on fifteen plates now containing raffinose as the sole carbon source. After repeating this process over five weeks, an average respiration loss for this carbon source was determined. The goal of using raffinose rather than dextrose was to determine how these two different carbon sources affected rates of respiration loss.

Raffinose is an oligosaccharide, meaning it consists of galactose, fructose, and glucose. Using raffinose rather than dextrose, provides more sugar alternatives than just dextrose, allowing for a smaller chance of fermentation happening. The yeast has the options of galactose, fructose, and glucose to utilize for cellular respiration to produce carbon dioxide, compared to dextrose only offering glucose as the sugar.

Figure 6: Effect of YPRaf on Respiration Loss

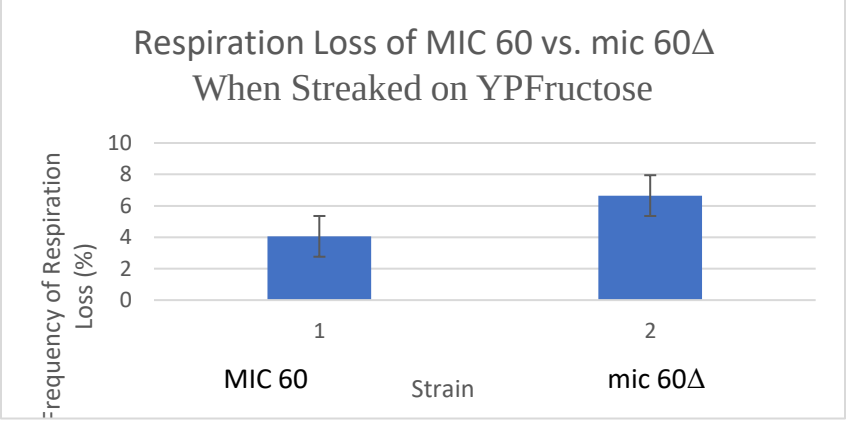


The results of how raffinose effects respiration loss can be seen above in Figure 6 and Table 3. Continuing the importance of *mic 60Δ* in a functional mitochondrion, the wild-type

shows a median of 5.8388978% respiration loss. The *mic 60Δ* shows a median of 8.511542% respiration loss. The mutant strain demonstrated a 1.46-fold increase to 8.51% in spontaneous respiration loss compared to the 5.84% observed in the wild-type. Cells in this particular strain of yeast are better-able to repair themselves using DNA repair mechanisms when raffinose is the sole carbon source rather than dextrose.

Fructose, the next carbon source used, is a monosaccharide that when bonded with glucose, forms sucrose. More importantly, fructose is used during respiration to produced ATP and build glycogen. It is produced by photosynthesis from the breakdown of glycogen. Saccharomyces cerevisiae thrives with the presence of glucose, because fructose is often depleted first, causing a smaller quantity of cells formed on the plates.

Figure 7: Effects of YPFructose on Respiration Loss



The results of how fructose affects cellular respiration loss can be seen in Figure 7. Continuing to reveal the importance of *mic60Δ* in a functional mitochondrion, the wild-type shows a median of 4.0584318% respiration loss. The *mic60Δ* shows a median of 6.653164% respiration loss. The mutant strain demonstrated a 1.64-fold increase to 6.653% in spontaneous respiration loss compared to the 4.058% observed in the wild-type, as seen in Figure 7 and Table

3. When fructose is the sole carbon source available, the cells are best able to repair themselves using DNA repair mechanisms.

Table 3. % Respiration Loss of MIC60 vs. mic60Δ

Carbon Source	*MIC60* (% respiration loss)	Mic60Δ (% respiration loss)	Fold change (mutant/w.t)
YPDextrose	5.08%	10.44%	2.05
YPRaffinose	5.84%	8.51%	1.46
YPFructose	4.058%	6.653%	1.64

Discussion

The overarching goal of this research was to determine the spontaneous respiration loss in *Saccharomyces cerevisiae* using three different carbon sources. Using fructose, the mutant strain demonstrated a 1.64-fold increase to 6.653% in spontaneous respiration loss compared to the 4.058% observed in the wild-type. Using raffinose, the mutant strain demonstrated a 1.46-fold increase to 8.51% in spontaneous respiration loss compared to the 5.84% observed in the wild-type. Using dextrose, the mutant strain demonstrated a 2.05-fold increase to 10.44% in spontaneous respiration loss compared to the 5.08% observed in the wild type strain. Comparing the results from YPDextrose, YPRaffinose, and YPFructose, raffinose as the carbon source produces the lowest fold change. However, fructose as the carbon source gives the lowest overall respiration loss in both the wild type and mutant strains. Conversely, dextrose as the carbon source produced the highest fold increase in cellular respiration loss between the wild type and mutant strains. Additionally, plates containing dextrose had the highest percentage of *rho*- cells

in the *mic60Δ* and the second highest respiration loss in the *MIC60* strain. This indicates that dextrose allowed more mutations in the mitochondrial DNA of both strains. Cells were not able to repair themselves as well using dextrose as they were with fructose and raffinose.

Using YPDextrose as the sole carbon source yielded the highest fold change. The *MIC60* wild-type strain produced a 5.08% respiration loss compared to the 10.44% respiration loss in the *mic60Δ* mutant strain. With a 2.05% increase in respiration loss between wild-type and mutant strains, dextrose is not the most successful carbon source. Using YPFructose as the sole carbon source yielded a significantly lower fold change. The *MIC60* wild-type strain produced a 4.058% respiration loss compared to the 6.653% respiration loss in the *mic60Δ* mutant strain. With a 1.64% increase in respiration loss between the wild-type and mutant strains, fructose is a better carbon source than dextrose. Using YPRaffinose as the sole carbon source produced the lowest fold change. The *MIC60* wild-type strain produced a 5.84% respiration loss compared to the 8.51% respiration loss in the *mic60Δ* mutant strain. With a 1.46% increase in respiration loss between the wild-type and mutant strains, raffinose is the best choice of carbon source for cellular respiration. This data also shows that Mic60p plays a vital role in maintaining mitochondria genome stability which is required for cellular respiration.

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