Mitochondria
The Hemi of the Cell

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ABSTRACT
There are many organelles within a cell, each with individual responsibilities required for life. Of these organelles, the mitochondria are the hemi of the cell, producing the energy necessary for cell function. Reactive oxygen species can cause mitochondrial dysfunction and contribute to many diseases often seen in emergency departments. When reactive oxygen species are produced, the mitochondria undergo functional and structural changes causing the release of cytochrome c. Cytochrome c is responsible for activating apoptotic pathways leading to cell death. Apoptosis, or programmed cell death, is needed to maintain homeostasis in the body; however, when this occurs prematurely by an increase in reactive oxygen species production, many pathological conditions can occur. Clinicians in emergency departments caring for patients with different diseases should consider that the mitochondria may play an important role in patients’ recovery. For instance, myocardial infarctions and burns are two examples of altered physiologic states that play a role in mitochondrial dysfunction. Awareness of the different treatments that target the mitochondria will prepare emergency department clinicians to better care for their patients. Key words: apoptosis, free radicals, mitochondria

OXIDATIVE STRESS is involved with many diseases such as emphysema, myocardial infarction (MI), and stroke (Anderson, Seed, Ou, & Harris, 1999; Hill & Singal, 1996; Leinonen et al., 2000).

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Oxidative stress occurs when the production of free radicals in the body exceeds the ability to eliminate them or by a reduction in antioxidants. Free radicals react with different organelles of the cell, particularly the mitochondria. The mitochondria are often forgotten about in nursing practice yet are an essential source of energy and metabolism and play a role in several different disease processes. Reactive oxygen species (ROS) are free radicals that affect the mitochondria. When there is an increase in ROS formation, cellular damage often occurs resulting in dysfunction to the mitochondria (Murphy & Smith, 2000; Picczenik & Neustadt, 2007). The damaged mitochondria trigger a release of cytochrome c through the mitochondrial...
pores (Yang et al., 1997). Once the cytochrome c is released, this commits the cell to die (Green & Reed, 1998). Cytochrome c is involved in the signaling of apoptosis, and when released prematurely, the result is often disease.

Programmed cell death (apoptosis) has been linked to many pathophysiologic states and is an important issue in clinical practice and research (Reed, 2002). This article reviews the structure and function of different organelles, particularly the mitochondria, as well as the importance of pharmacological treatments that target the mitochondria such as taking ubiquinone (coenzyme Q10 [CoQ10]). An in-depth understanding and recognition of the importance of mitochondria will assist clinicians in understanding, preventing, and treating diseases often observed in the emergency department (ED).

**Table 1.** Description of selected organelles of the cell

<table>
<thead>
<tr>
<th>Organelle</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>Actin</td>
<td>A protein located in the microtubule, involved in contraction of the muscle and cell division, motility, and signaling.</td>
</tr>
<tr>
<td>Cytosol</td>
<td>The fluid component of cytoplasm in which all organelles are located.</td>
</tr>
<tr>
<td>Endoplasmic reticulum</td>
<td>Tubular network of membranes that is responsible for transportation of chemicals throughout the cell.</td>
</tr>
<tr>
<td>Golgi complex (apparatus)</td>
<td>Stacks of membrane-bound vesicles and vacuoles that lie adjacent to the nucleus that package molecules for transport.</td>
</tr>
<tr>
<td>Lysosome</td>
<td>Small and round organelles that are responsible for digestion of cell waste.</td>
</tr>
<tr>
<td>Mitochondria</td>
<td>Membrane-bounded organelles that are responsible for adenosine triphosphate synthesis essential to metabolism of the body.</td>
</tr>
<tr>
<td>Nucleolus</td>
<td>Spherical in shape, produces and assembles ribosome components.</td>
</tr>
<tr>
<td>Nucleus</td>
<td>Large, oval-shaped organelle that contains deoxyribonucleic acid. It is responsible for processing cell information and controls cell activities such as growth and protein synthesis.</td>
</tr>
<tr>
<td>Peroxisome</td>
<td>An organelle that contains enzymes that are responsible for molecule import and removal of toxins within the cell.</td>
</tr>
<tr>
<td>Plasma membrane</td>
<td>A selectively permeable outer layer made of proteins, provides transportation of ions and protection to the cell.</td>
</tr>
<tr>
<td>Tubulin (α-tubulin and β-tubulin)</td>
<td>Globular proteins that make up the microtubules that assist in cell support.</td>
</tr>
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**CELL STRUCTURE AND FUNCTION**

Billions of cells that vary in size and shape make specialized tissues and organs possible. Many drugs target specific cell structures, making the significance of organelle knowledge great to those administering medications. Most cells are surrounded by a plasma membrane and contain a nucleus and multiple organelles. Table 1 is a review of the structure and function of some selected organelles in a cell. Organelles within the cell are surrounded by membranes that allow for segregation and communication. Figure 1 is an illustration of the different organelles within the cell. Each organelle has a function that accounts for the cell’s viability; however, the mitochondrion is a small organelle with immense responsibilities including generation of cellular energy and respiration (Wallace, 1999).
Structurally, the mitochondria are thread-shaped organelles that are compartmentalized, with an outer membrane surrounding an inner membrane folded into fingerlike objects called cristae (Murphy & Smith, 2000). Cristae have layers called lamellae that increase surface area and reduce transport time (Mannella, 2006; Paumard et al., 2002). The porous outer membrane is made of protein structures and is permeable to smaller molecules because of its phospholipid bilayer. The convoluted inner membrane contains enzymes and metabolic pathways that assist in adenosine triphosphate (ATP) production. The outer and inner membranes generate the intermembrane space that contains many proteins that are essential in metabolic pathways. The viscous matrix space of the mitochondria contains ribosomes, enzymes, and proteins that are necessary for different metabolic pathways such as the citric acid cycle (Murphy & Smith, 2000). Figure 2 illustrates a mitochondrion with the outer and inner membranes, cristae, and matrix space. The mitochondria function as the hemi of the cell, much of the oxygen taken in during respiration is used by the mitochondria to produce energy needed by the cell (Murphy & Smith, 2000). Hemi is an abbreviation for an engine whose combustion chamber is hemispherical to produce a more even burning of fuel, which makes the engine more powerful. Thus, the hemi of the cell refers to the mitochondria, which are the energy-producing structure of cells.

Figure 1. The cell and some of the organelles in a three-dimensional view. Reproduced with permission from Invitrogen, Carlsbad, CA.

Figure 2. The mitochondria: inner and outer membranes, the cristae, and the matrix space. From *Pathophysiology: Concepts of Altered Health States* (6th ed., p. 68), by C. M. Porth, 2002, Philadelphia: Lippincott Williams & Wilkins. Copyright 2002 by Lippincott Williams & Wilkins. Reproduced with permission.
MITOCHONDRIA AND DISEASE

Reactive Oxygen Species

During the normal metabolism of oxygen in the mitochondria, ROS are produced as byproducts. ROS are a reduction–oxidation derivative of molecular oxygen and are highly reactive molecules that play an important role in cell signaling (Murrant & Reid, 2001). ROS are highly reactive because they have unpaired electrons in the valence shell. Examples of ROS include superoxide, hydrogen peroxide, and hydroxyl radicals. ROS play a role in cytotoxicity through alterations in protein, lipid, and nucleic acid structure and function (Tarpey, Wink, & Grisham, 2004). Alterations occur by a posttranslational reduction–oxidation modification based on the level of ROS exposure in proteins and oxidization in lipids and nucleic acids (Forrester & Stamler, 2007). ROS levels increase during times of stress, and the result may be damage to the mitochondria’s structure and function.

Cytochrome C

When a person is under stress, many substances are released including a protein called p66shc. This protein takes electrons from the mitochondrial cytochrome c and uses them to produce hydrogen peroxide (Orsini et al., 2006). If ROS production is too great, mitochondria lose the ability to synthesize ATP, and this leads to dysfunction of the sodium–potassium pump on the cell membrane. This results in cell swelling and the release cytochrome c, which leads to activation of caspases and induction of apoptosis (Wakabayashi, 2002). Cytochrome c, a component of the mitochondrial electron transport chain, initiates caspase activation when released from the mitochondria (Liu, Kim, Yang, Jemmerson, & Wang, 1996; Wang, 2001). Caspases are proteins that can affect cytosolic and nuclear substrates resulting in apoptosis (Green & Reed, 1998). Cytochrome c, even without the overproduction of ROS, is released to cause cell death in response to deoxyribonucleic acid (DNA) damage or infection (Skulachev, 1998).

Apoptosis

Apoptosis is a programmed cell death that naturally occurs in the body to maintain homeostasis. Multiple apoptotic pathways are stimulated by mitochondrial activity (Wang, 2001). When there are disruptions in this pathway, apoptosis may occur more or less frequently than normal, causing pathologic problems (Murphy & Smith, 2000). During certain phases of apoptosis, uncoupling of the mitochondria occurs and is followed by DNA degradation (Kroemer, Petit, Zamzami, Vayssiere, & Mignotte, 1995). In addition, metabolic changes may occur within the mitochondria during apoptosis, resulting in enzymatic reactions that directly impact mitochondrial function (Wang, 2001). As a result, cellular defects occur that may lead to various disease states (Wallace, 1999).

Mitochondrial DNA Mutation

Mitochondrial DNA (mtDNA) mutation can be the cause for many diseases as well (Clayton, 1991). The mtDNA is circular, small, and simple compared with nucleic DNA (Murphy & Smith, 2000; Wallace, 1999). An interesting detail about mtDNA mutation and disease is that with more mutated nuclei, more severe clinical symptoms will be seen (Lightowlers, Chinnery, Turnbull, & Howell, 1997). ATP production can be decreased with mtDNA mutation; therefore, cells that depend on mitochondrially generated ATP are at the greatest risk for disease (DiMauro & Schon, 2001). Many patients who are admitted to the ED have clinical conditions from mitochondrial dysfunction caused by ROS and mtDNA damage (Murphy & Smith, 2000; Picczenik & Neustadt, 2007; Tarpey et al., 2004).

Other Substances That Accelerate Mitochondrial Damage

There are other substances that have been demonstrated to accelerate some mitochondrial disorders. The two most common are
alcohol and cigarette smoke. Alcohol promotes calcium activation of the mitochondrial permeability pore, resulting in cytochrome c release and subsequent apoptosis (Hajnoczky, Buzas, Pacher, Hoek, & Rubin, 2005). With cigarette smoke, the carbon monoxide destroys the mitochondria by inhibiting Complex IV of mitochondrial oxidative phosphorylation (Gvozdjakova et al., 1984; Leone, Landini, Biadi, & Balbarini, 2008).

Surprisingly, a treatment frequently used in the ED has been shown to cause mitochondrial damage—too much oxygen. When cells are exposed to hyperoxia, there is an abundance of free radicals, which can induce extensive mitochondrial damage (Pagano, Donati, Metrailler, & Barazzone Argiroffo, 2004; Scatena et al., 2004). Of course, too little oxygen, hypoxia, also results in anaerobic metabolism and decreased ATP production by the mitochondria.

**CLINICAL SIGNIFICANCE**

One of the first articles about mitochondrial medicine in emergency medicine was about the role of mitochondria and emphasized the importance of emergency medicine personnel understanding mitochondrial dysfunction and treatment therapies (Watts & Kline, 2003). All of the major organs of the body require a substantial amount of energy to perform their functions, so it is not surprising that serious illness can be the result or the cause of mitochondrial dysfunction (Murphy & Smith, 2000).

**Disease Processes That Cause Mitochondrial Dysfunction**

As adults age, they may develop severe defects of mitochondrial function, leading to different disease states. These include cancer, Type 2 diabetes, atherosclerotic heart disease, transient ischemic attacks, Alzheimer’s disease, and Parkinson’s disease. Furthermore, mitochondria can be damaged by medications such as simvastatin, haloperidol, and captopril (Gasademont et al., 2007; Gvozdjakova et al., 1999; Schick et al., 2007). While mitochondrial-specific diseases are now being discovered, it still remains a challenge to confirm diagnoses due to mitochondrial DNA mutations because of the complexities of the genotype-phenotype correlations (Wong, 2007). When there is damage to the mitochondria, organs will be affected and disease will occur. Certain pharmacological treatments are used to target the mitochondria because of their role in energy metabolism, ROS production, and apoptosis. For example, atenolol and carvedilol have been shown to have antioxidant effects and inhibit mitochondrial cytochrome c release, which may reduce overall mortality and decrease heart failure-related cell damage (Lechat et al., 1998; Packer et al., 1996; Romeo, Li, Shi, & Mchta, 2000). Thus, when these drugs are ordered, personnel administering these treatments need to understand on a cellular level what might be occurring. A common example of a disease that is observed by healthcare professionals in the ED is MI.

Research has indicated that during myocardial injury the mitochondrial structure and function are abnormal (Marin-Garcia & Goldenthal, 2002; Zang, Maass, White, & Horton, 2007). During the ischemic process, mitochondrial ROS production increases and oxidative stress occurs (Shohet & Garcia, 2007; Zorov, Filburn, Klotz, Zweier, & Sollott, 2000). An MI is preceded by increased ROS and decreased ATP production within the mitochondria, leading to apoptosis (Webster et al., 2006). To decrease the amount of ROS produced during an MI, antioxidant therapy targeting the mitochondria could be beneficial in preventing an overabundance of oxidative stress and further damage. Currently, there are many therapies being tested in humans to reduce myocardial injury such as antioxidants, caspase inhibitors, insulin-like growth factor-1, and calcium-channel blockers (Khoynezhad, Jalali, & Tortolani, 2004; Ratnam, Ankola, Bhardwaj, Sahana, & Kumar, 2006).

Another condition commonly treated in the ED is burns. In any burn, oxidative stress
occurs; however, in a severe burn it could be the major factor contributing to organ failure (Horton, 2003). Studies have shown that to decrease burn-related immunosuppression and improve the function of the organs after a burn, antioxidant therapy should be used (Cetinkale, Senel, & Bulan, 1999; Tauskela, 2007). A study on the beneficial effects of antioxidant therapy found that antioxidant vitamin therapy prevented cardiac dysfunction by preventing the loss of mitochondrial membrane integrity related to the burn (Zang et al., 2007).

Diabetes is another disease associated with mitochondrial dysfunction (Nisoli, Cozzi, & Carruba, 2008; Schrauwen & Hesselink, 2004). Type 2 diabetes is associated with mitochondrial dysfunction, suggesting that prevention and treatment should focus on the mitochondrial targets (Wiederkehr & Wollheim, 2006). Mitochondrial ROS increase in response to hyperglycemia, which can lead to complications such as renal disease (Forbes, Coughlan, & Cooper, 2008). In skeletal muscle, patients with diabetes have a lower mitochondria population, which helps to explain the decrease in rates of oxidative phosphorylation (Civitarese & Ravussin, 2008). Investigators have found that lifestyle changes can increase the number of mitochondria and help control diabetes (Toledo et al., 2007, 2008).

**Diseases Resulting From Mitochondrial Mutation**

There are many specific mitochondrial diseases, such as diabetes mellitus, Huntington’s chorea, and primary biliary sclerosis, to name a few. The United Mitochondrial Disease Foundation (UMDF) was started to support all sufferers of mitochondrial disorders. The Foundation’s Web site lists over 50 mitochondrial diseases and describes how these diseases are related to mitochondrial defects or injury (UMDF, n.d.). These mitochondrial diseases directly affect the mitochondria and are caused by DNA mutation. However, the production of ROS inside the mitochondria as well as frequent DNA mutations links the mitochondria to multiple diseases and cancers (Klaunig & Kamendulis, 2004).

Thermal regulation may not be normal in patients with mitochondrial diseases, and exposure to cold can result in severe heat loss (Farhadi et al., 2005; Tanaka, Takeyasu, Fuku, Li-Jun, & Kurata, 2004). Conversely, exposure to heat can lead to heat exhaustion and heat stroke because some patients with mitochondrial diseases cannot sweat normally (Clay, Behnia, & Brown, 2001).

**Therapies**

Ubiquinone, also called CoQ10, is used as a dietary supplement and acts as an antioxidant by reducing ROS production and thus mitochondrial damage (Crane, 2001; Dallner & Sindelar, 2000). Ubiquinone is present in most human cells and is responsible for the production of ATP. With the assistance of ubiquinone, glucose is converted to ATP in the mitochondria. Ninety-five percent of ATP is converted with the help of ubiquinone (Ernster & Dallner, 1995). Therefore, organs with the highest energy requirements will have the highest ubiquinone concentrations (Aberg, Appelkvist, Dallner, & Ernster, 1992; Okamoto, Matsuya, Fukunaga, Kishi, & Yamagami, 1989; Shindo, Witt, Han, Epstein, & Packer, 1994). In the clinical setting, ubiquinone is now being used to treat metabolic disorders, as well as serious mitochondrial diseases (Berbel-Garcia et al., 2004). Ubiquinone has been found to have beneficial effects on patients who suffer from migraine headaches, MI, and cancer (Rozen et al., 2002; Sandor et al., 2005). For those with low levels of ubiquinone, this substance offers a prophylactic effect that provides the mitochondria with the ability to create enough ATP (Haas, 2007; Littarru & Tiano, 2007). Mitocinone mesylate (MitOQ®) is an antioxidant that can target mitochondrial dysfunction. When delivered to the intracellular region where increased levels of ROS are present, mitocinone mesylate functions similar to ubiquinone (Tauskela, 2007).
Mitoquinone mesylate has been accepted by the United States Food and Drug Administration for use in clinical trials; future approval is anticipated and may lead to use in EDs. In Phase II clinical trials in patients with liver diseases, mitoquinone mesylate (40–80 mg PO) was administered once a day with no reported adverse effects (Tauskela, 2007).

Other antioxidants scavenge free radicals and help prevent mitochondrial damage. These include vitamin C, vitamin E, lycopene, and α-lipoic acid (McMackin et al., 2007; Ratnam et al., 2006). For example, vitamin C has been shown to reduce mitochondrial damage in congestive heart failure (Rossig et al., 2001). Administering vitamin E to patients with Type 2 diabetes decreases mitochondrial damage (Faure, 2003).

**CONCLUSION**

Many patients admitted to the hospital are first assessed in the ED. To effectively prevent further cellular damage and treat these patients, an understanding of cell biology is necessary to comprehend the therapeutic effects of clinical treatment. Injured patients will have an abundance of ROS production, resulting in damage to the mitochondria's structure and function. When this damage occurs, cytochrome c is released, resulting in the initiation of apoptotic caspases that ends in cell death and disease. ED clinicians should recognize the importance of maintaining mitochondrial function as part of preventative care and optimizing the patient's health. This allows the mitochondria to produce ATP and fulfill its duty as the hemi of the cell.

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