For the pursuit of oxygen and carbon dioxide channels in mitochondria

Respiratory gas exchange is a vital activity for many organisms including human being. Through respiration, carbon dioxide (CO_2) is exhaled for the exchange of oxygen (O_2) from the air. At the cellular level, O_2 is used to convert biochemical energy from nutrients into adenosine triphosphate (ATP) with the production of CO_2. In the resting state, a healthy adult consumes about 550 L of pure oxygen and produces over 2 pounds (~0.91 kg) of CO_2 every day (Jequier et al., 1987). Given that continuous production of ATP is absolute essential for both cell survival and conduction of normal cellular function, exchange of O_2 and CO_2 at both the respiratory and cellular levels is critical.

The mitochondrion is the powerhouse of cells that performs most cellular oxidations and produces majority of ATP (Cheng et al., 2015; d'Esterre et al., 2015; Jing et al., 2015; Shenoda, 2015; Alhadidi et al., 2016). Mitochondria are unusual organelles with two membranes and their own genome. It is believed that the mitochondrial outer membrane has many protein-based pores that are big enough to allow the passage of ions and molecules as large as small proteins. On the other hand, the inner membrane has much more restricted permeability as the plasma membrane of the cell (Mannella, 1992). As the site for main cellular respiration processes of citric acid cycle and oxidative phosphorylation, mitochondria matrix are not only the final destiny for O_2 but also the site for CO_2 production. O_2 and CO_2 have to be transported across the cellular membrane, the inner and outer mitochondrial membrane to reach the destiny or release out of the cell.

The classical concept of the plasma membranes is extremely permeable to gases, which has been extended to the solubility-diffusion mechanism for the gas transport across plasma membrane, including O_2 and CO_2 (Finkelstein, 1976; Harch, 2015; Katz et al., 2015; Langston and Toombs, 2015; Parra et al., 2015; Stoller, 2015). It is generally believed that both O_2 and CO_2 molecules are transport across the plasma membrane through diffusion. Nonetheless, the O_2 permeability coefficient for the plasma membrane has been found to be two times lower than that for a water layer of the same thickness as the membrane (Subczynski et al., 1992). Furthermore, plasma membrane has been found to be even less permeable for CO_2 (Boron et al., 1994; Waisbren et al., 1994; Endeward and Gros, 2005). Thus, trans-membrane CO_2 and O_2 channels might serve as an alternative mechanism to increase the permeability of O_2 and CO_2 cross the plasma membrane. In the last two decades, an increasing evidence has been emerged that aquaporin (APQ) may serve as plasma membrane CO_2channels including AQP1, AQP4, and AQP5 with varied affinities (Herrera and Garvin, 2011; Endeward et al., 2014). On the other hand, pursuing membrane O_2 channel has been even more elusive (Endeward et al., 2014).

The unique double membrane structure of mitochondria creates even a greater barrier for the cross membrane transport of CO_2 and O_2. Ironically, much less effort has been invested for the pursuit of mitochondrial membrane channels for O_2 and CO_2. Water is one of the major end products of mitochondrial oxidative phosphorylation. Therefore it might not be a surprise that the mitochondrial membrane express extensive water channels. Osmotic swelling is one of the fundamental features exhibited by mitochondria in pathological conditions (Halestrap, 1989). The mitochondrial permeability transition pore (MPTP) has been indicted to permit the passage of molecule of mass < 1.5 kDa in a nonselective manner including water, thus, has long been postulated to be the primary mediator for water movement in term of mitochondrial swelling. However the molecular identity of MPTP remains obscure. The discovery of the expression of APQ channels, AQP8 and 9, in the mitochondria inner membrane indicated that APQs may function as transporters for water and CO_2 trafficking in the mitochondria (Lee and Thevenod, 2006). Otherwise, no other potential gas channel has been identified in mitochondria for the trans-membrane transport of CO_2 and O_2. CO_2 molecule is distinct from O_2 molecule in the difference of plasma membrane permeability and solubility. The absolute solubility of CO_2 in both water and lipid are more than an order of magnitude greater than those of O_2 (Endeward et al., 2014). Therefore, it is plausible that CO_2 is transported across cellular as well as mitochondrial membrane *via* different mechanisms from O_2. Nevertheless, identification of the precise mechanism underlying the transportation of O_2 and CO_2 crossing mitochondrial membranes will provide significant insights for our understanding of mitochondria function and its role in both physiological and pathological conditions. With the limited achievement of the plasma CO_2 channels, the pursuit of mitochondrial gas channels will have a long way to go.

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