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Powerhouse down: Complex II dissociation in the respiratory chain

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ABSTRACT

Complex II of the respiratory chain (RC) recently emerged as a prominent regulator of cell death. In both cancer cells as well as neurodegenerative diseases, mutations in subunits have been found along with other genetic alterations indirectly affecting this complex. Anticancer compounds were developed that target complex II and cause cell death in a tumor-specific way. Our mechanistic understanding of how complex II is activated for cell death induction has recently been made clearer in recent studies, the results of which are covered in this review. This protein assembly is specifically activated for cell death via the dissociation of its SDHA and SDHB subunits from the membrane-anchoring proteins through pH change or mitochondrial Ca^{2+} influx. The SDH activity contained in the SDHA/SDHB subcomplex remains intact and then generates, in an uncontrolled fashion, excessive amounts of reactive oxygen species (ROS) for cell death. Future studies on this mitochondrial complex will further elucidate it as a target for cancer treatments and reveal its role as a nexus for many diverse stimuli in cell death signaling.

1. Complex II structure and function

The mitochondrial respiratory chain is made up of four membrane-bound, multimeric protein complexes anchored to the inner mitochondrial membrane (IMM). These complexes all assist in catalyzing the oxidation of reducing equivalents, primarily NADH, using molecular oxygen as the terminal electron acceptor (Fig. 1) (Lenaz and Genova, 2010). Respiratory chain-mediated electron transfer is connected to the final complex, ATP synthase or complex V, which is responsible for generating ATP. The coupling effect between the respiratory chain and ATP production is known as oxidative phosphorylation. All respiratory chain complexes consist of protein aggregates made up of encoded factors from nuclear and/or mitochondrial DNA.

Complex II consists of four subunits: SDHA, SDHB, SDHC, and SDHD. The smallest complex in the respiratory chain and the only one to be entirely made of nuclear-encoded DNA, it is an entry point for reducing equivalents, along with complex I, generated from the oxidation of succinate to fumarate within the tricarboxylic acid (TCA) cycle (Fig. 2). Electrons from complex II reduce coenzyme Q to ubiquinol before continuing down the respiratory chain. Additionally, this complex is unique because it is the only one that doesn't contribute to pumping protons across the IMM (Rutter et al., 2010). Based on the crystal structure of complex II and a schematic representation, SDHC and SDHD are hydrophobic subunits anchored to the IMM (Fig. 2) (Sun et al., 2005; Yankovskaya et al., 2003). The transmembrane domains of SDHC and SDHD consist of heme *b*, a potential redox group whose function within complex II has been defined as a protein-bound prosthetic group (Kim et al., 2012). It has been suggested that this redox group has a structural role in stabilizing the two hydrophobic subunits, however this is still controversial. Other possibilities include involvement in transmembrane electron transfer and/or the preventions of reactive oxygen species formation during electron transfer from FAD to ubiquinone by acting as a capacitor during high electron flux (Yankovskaya et al., 2003). Ultimately, its specific role in the transfer of electrons within complex II is so far unverified (Lemarie and Grimm, 2009; Oyedotun et al., 2007).

The SDHB subunit has been shown in eukaryotic cells to be associated with the hydrophobic, membrane-anchored subunits SDHC and SDHD. Together with SDHA, SDHB forms the hydrophilic group responsible for oxidizing succinate to fumarate in the TCA cycle as the catalytic core of complex II. Within the hydrophobic sub-complex, electrons are transported from the FAD cofactor in SDHA to the three [Fe–S] clusters located in SDHB (Fig. 2) (Rutter et al., 2010; Sun et al., 2005). The enzymatic activity of this part of complex II is known as the succinate dehydrogenase (SDH) activity (Fig. 3) (Lemarie et al., 2011). The SDHC and SDHD junction consists of two CoQ-binding sites which are Q_P (proximal to the iron sulfur clusters) and Q_D (distal to the iron sulfur clusters) (Rutter et al., 2010; Sun et al., 2005). An incomplete formation of the reduced semiquinone is produced by the first electron transfer. By the second electron transfer, with the production of ubiquinol, the semiquinone radical is stabilized for complete reduction (Guo and Lemire, 2003; Rutter et al., 2010). This two-step process is a mechanism that protects the complex from excessive electron leakage. The electron

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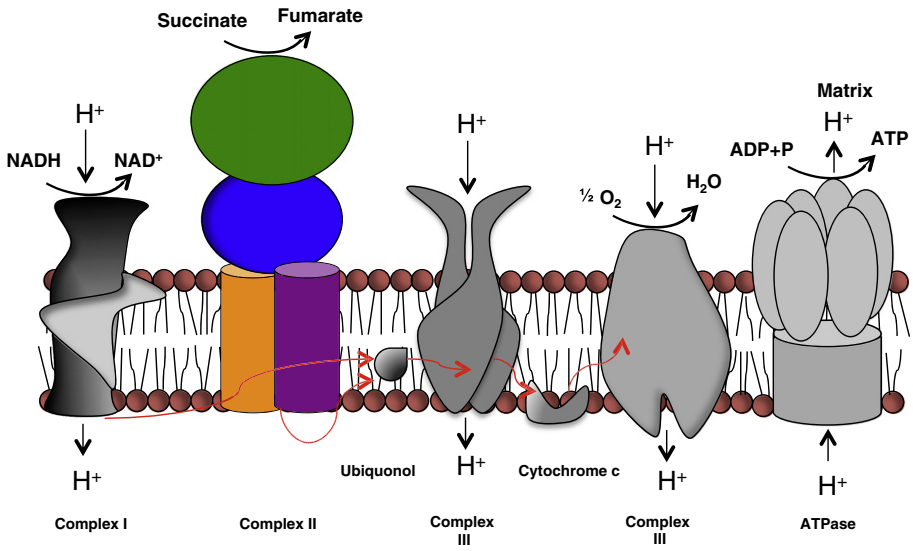

Fig. 1. Schematic representation of the mitochondrial respiratory chain complexes and the oxidative phosphorylation system. The four complexes of the respiratory chain and the ATP synthase are outlined with the respective electron/proton pathways along the complexes shown. Complex II is highlighted in color.
Adapted from Grimm (2013).

transfer in complex II beginning from succinate and ending at the Q_P site makes up the succinate CoQ oxidoreductase (SQR) activity. This has been measured via an enzymatic assay (Lemarie et al., 2011).

2. Complex II in apoptosis

The connection between complex II and apoptotic cell death emerged only recently based on its role in Leigh syndrome or Subacute Necrotizing Encephalomyelopathy (SNEM), a neurodegenerative disease that influences the central nervous system and is associated with neuronal cell death, eventually resulting in impaired motor functions (Finsterer, 2008). This link was established via investigations on mutations in SDHA, which were connected to the disease (Bourgeron et al., 1995). Many studies involving neuronal cells have displayed pro-apoptotic effects upon specific complex II inhibition (McLaughlin et al., 1998; Pang and Geddes, 1997). This has been observed when using the irreversible complex II inhibitor thenoyltrifluoroacetone (TTFA), which binds at the quinone reduction site in Complex II, preventing ubiquinone from binding and ultimately inhibiting the SQR activity. 3-Nitropropionic acid (3-NP) and the competitive inhibitor methylmalonate are both reagents that target the succinate-binding site in SDHA, specifically inhibiting the SDH activity, but achieving an anti-apoptotic effect by abrogating the effect of TTFA (Brusque et al., 2002; Grimm, 2013; Lemarie et al., 2011). The tumor-suppressor gene function of SDHB, SDHC and SDHD subunits was discovered as most prominent indications that complex II is involved in apoptosis regulation (Astuti et al., 2001; Baysal et al.,

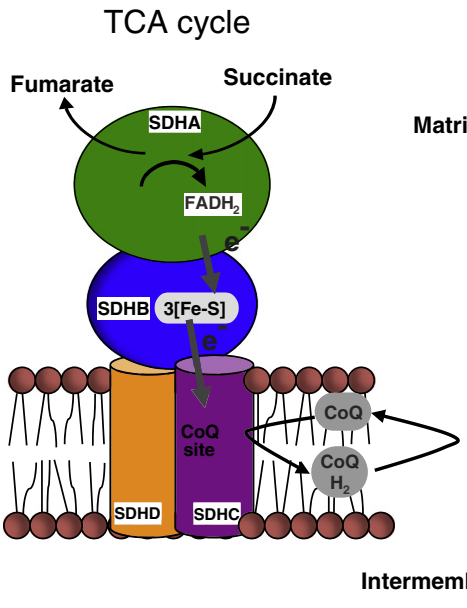

Fig. 2. Complex II structure and function. The four subunits of the complex are shown, the SDHA and SDHB hydrophilic subunits along with SDHC and SDHD hydrophobic subunits anchored to the inner mitochondrial membrane. The electron flow of reducing equivalents generated from the oxidation of succinate to fumarate, coupled with the reduction of FAD to $FADH_2$, is shown.
Adapted from Grimm (2013).

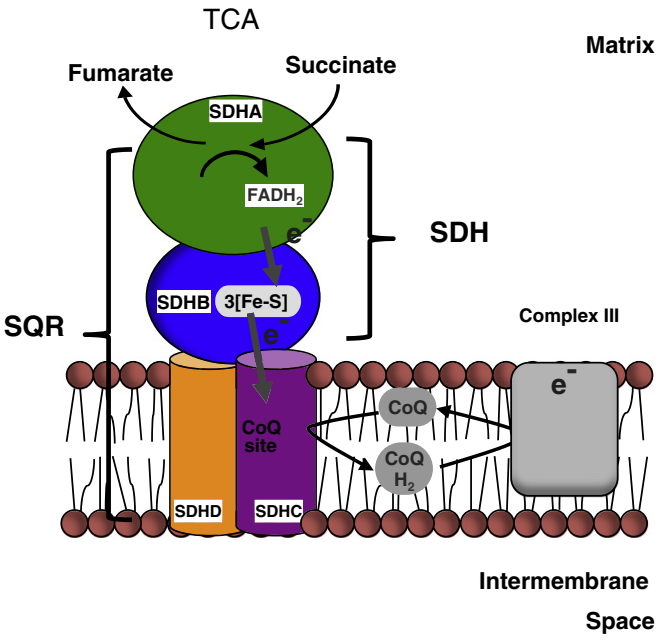

Fig. 3. Complex II succinate dehydrogenase (SDH) and succinate CoQ oxidoreductase (SQR) activities. SDH activity is defined as the flow of electrons from the FAD cofactor in SDHA to the three [Fe–S] clusters located in SDHB. SQR activity is defined as the flow of electrons from succinate and ending at the Q_P site.
Adapted from Grimm (2013).