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Consortium communication

Mitochondrial physiology
1. Mitochondria and bioblasts

MitoEAGLE Task Group*

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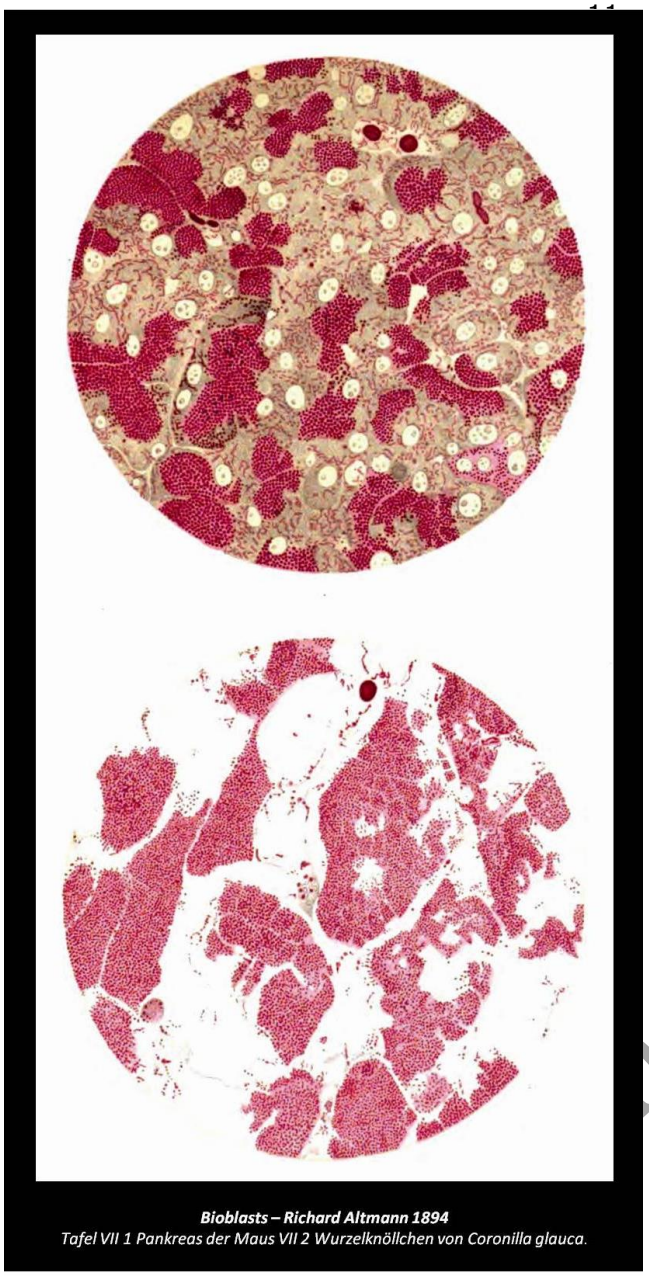

Overview

Richard Altmann (1894):

The protoplasm is a colony of bioblasts. Microorganisms and granula are at an equivalent level and represent elementary organisms, which are found wherever living forces are acting, thus we want to describe them by the common term bioblasts. In the bioblast, that morphological unit of living matter appears to be found.

Mitochondria are oxygen-consuming electrochemical generators that evolved from the endosymbiotic alphaproteobacteria which became integrated into a host cell related to Asgard Archaea (Margulis 1970; Lane 2005; Roger *et al* 2017). Richard Altmann (1894) described the 'bioblasts', which include not only the mitochondria as presently defined, but also symbiotic and free-living bacteria. The word 'mitochondria' (Greek mitos: thread; chondros: granule) was introduced by Carl Benda (1898). Mitochondrion is singular and mitochondria is plural. Abbreviation: mt, as generally used in mtDNA.

Given the multiple roles of mitochondria, it is perhaps not surprising that mitochondrial dysfunction is associated with a wide variety of genetic and degenerative diseases. Robust mitochondrial function is supported by physical exercise and caloric balance, and is central for sustained metabolic health throughout life. Therefore, a more consistent set of definitions for mitochondrial physiology will increase our understanding of the etiology of disease and improve the diagnostic repertoire of mitochondrial medicine with a focus on protective medicine, evolution, lifestyle, environment, and healthy aging.

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Abstract

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Mitochondrial structure-function relationships

> '*For the physiologist, mitochondria afforded the first opportunity for an experimental approach to structure-function relationships, in particular those involved in active transport, vectorial metabolism, and metabolic control mechanisms on a subcellular level*' (Ernster and Schatz 1981).

Contrary to current textbook dogma, which describes mitochondria as individual organelles, mitochondria form dynamic networks within eukaryotic cells. Mitochondrial movement is supported by microtubules. Mitochondrial size and number can change in response to energy requirements of the cell via processes known as fusion and fission; these interactions allow mitochondria to communicate within a network (Chan 2006). Mitochondria can even traverse cell boundaries in a process known as horizontal mitochondrial transfer (Torralba *et al* 2016). Another defining morphological characteristic of mitochondria is the double membrane. The mitochondrial inner membrane (mtIM) forms dynamic tubular to disk-shaped cristae that separate the mitochondrial matrix, *i.e.*, the negatively charged internal mitochondrial compartment, from the intermembrane space; the latter being enclosed by the mitochondrial outer membrane (mtOM) and positively charged with respect to the matrix.

Intracellular stress factors may cause shrinking or swelling of the mitochondrial matrix that can ultimately result in permeability transition (mtPT; Lemasters *et al* 1998). The mtIM contains the non-bilayer phospholipid cardiolipin, which is also involved in the mtOM (Gebert *et al* 2009) but is not present in any other eukaryotic cellular membrane. Cardiolipin has many regulatory functions (Oemer *et al* 2018); it promotes and stabilizes the formation of supercomplexes ($SCI_nIII_nIV_n$) based on dynamic interactions between specific respiratory complexes (McKenzie *et al* 2006; Greggio *et al* 2017; Lenaz *et al* 2017), and it supports proton transfer on the mtIM from the electron transfer system to F_1F_O-ATPase (ATP synthase; Yoshinaga *et al* 2016). The mtIM is plastic and exerts an influence on the functional properties of incorporated proteins (Waczulikova *et al* 2007).

Mitochondria constitute the structural and functional elementary components of cell respiration (**Figure 1**). Mitochondrial respiration is the reduction of molecular oxygen by electron transfer coupled to electrochemical proton translocation across the mtIM. In the process of OXPHOS, the catabolic reaction of oxygen consumption is electrochemically coupled to the transformation of energy in the phosphorylation of ADP to adenosine triphosphate (ATP; Mitchell 1961, 2011). Mitochondria are the powerhouses of the cell that contain the machinery of the OXPHOS-pathways, including transmembrane respiratory complexes (proton pumps with FMN, Fe-S and cytochrome *b*, *c*, aa_3 redox systems); alternative dehydrogenases and oxidases; the coenzyme ubiquinone (Q); F_1F_O-ATPase or ATP synthase; the enzymes of the tricarboxylic acid cycle (TCA), fatty acid and amino acid oxidation; transporters of ions, metabolites and co-factors; iron/sulphur cluster synthesis; and mitochondrial kinases related to catabolic pathways. TCA cycle intermediates are vital precursors for macromolecule biosynthesis (Diebold *et al* 2019). The mitochondrial proteome comprises over 1,200 proteins (Calvo *et al* 2015; 2017), mostly encoded by nuclear DNA (nDNA), with a variety of functions, many of which are relatively well known, *e.g.,* proteins regulating mitochondrial biogenesis or apoptosis, while others are still under investigation, or need to be identified, *e.g.,* mtPT pore and alanine transporter. The mammalian mitochondrial proteome can be used to discover and characterize the genetic basis of mitochondrial diseases (Williams *et al* 2016; Palmfeldt and Bross 2017).

Mitochondrial crosstalk

Numerous cellular processes are orchestrated by a constant crosstalk between mitochondria and other cellular components. For example, the crosstalk between mitochondria and the endoplasmic reticulum is involved in the regulation of calcium homeostasis, cell division, autophagy, differentiation, and anti-viral signaling (Murley and Nunnari 2016). Mitochondria contribute to the formation of peroxisomes, which are hybrids of mitochondrial and ER-derived precursors (Sugiura *et al* 2017). Cellular mitochondrial homeostasis (mitostasis) is maintained through regulation at transcriptional, post-translational and epigenetic levels (Ling and Rönn 2018; Lisowski *et al* 2018), resulting in dynamic regulation of mitochondrial turnover by biogenesis of new mitochondria and removal of damaged mitochondria by fusion, fission and mitophagy (Singh *et al* 2018). Cell signalling modules contribute to homeostatic regulation throughout the cell cycle or even cell death by activating proteostatic modules, *e.g.*, the ubiquitin-proteasome and autophagy-lysosome/vacuole pathways; specific proteases like LON, and genome stability modules in response to varying energy demands and stress cues (Quiros *et al* 2016). In addition, several post-translational modifications, including acetylation and nitrosylation, are capable of influencing the bioenergetic response, with clinically significant implications for health and disease (Carrico *et al* 2018).

The mitochondrial genome

Mitochondria of higher eukaryotes typically maintain several copies of their own circular genome known as mitochondrial DNA (mtDNA; hundred to thousands per cell; Cummins 1998), which is maternally inherited in many species. However, biparental mitochondrial inheritance is documented in some exceptional cases in humans (Luo *et al* 2018), is widespread in birds, fish, reptiles and invertebrate groups, and is even the norm in some bivalve taxonomic groups (Breton *et al* 2007; White *et al* 2008). The mitochondrial genome of the angiosperm *Amborella* contains a record of six mitochondrial genome equivalents acquired by horizontal transfer of entire genomes, two from angiosperms, three from algae and one from mosses (Rice *et al* 2016). In unicellular organisms, *i.e.*, protists, the structural organization of mitochondrial genomes is highly variable and includes circular and linear DNA (Zíková *et al* 2016). While some of the free-living flagellates exhibit the largest known gene coding capacity, *e.g.*, jakobid *Andalucia godoyi* mtDNA codes for 106 genes (Burger *et al* 2013), some protist groups, *e.g.*, alveolates, possess mitochondrial genomes with only three protein-coding genes and two rRNAs (Feagin *et al* 2012). The complete loss of mitochondrial genome is observed in the highly reduced mitochondria of *Cryptosporidium* species (Liu *et al* 2016). Reaching the final extreme, the microbial eukaryote, oxymonad *Monocercomonoides*, has no mitochondrion whatsoever and lacks all typical nuclear-encoded mitochondrial proteins, showing that while in 99 % of organisms mitochondria play a vital role, this organelle is not indispensable (Karnkowska *et al* 2016).

In vertebrates, but not all invertebrates, mtDNA is compact (16.5 kB in humans) and encodes 13 protein subunits of the transmembrane respiratory Complexes CI, CIII, CIV and ATP synthase (F_1F_0-ATPase), 22 tRNAs, and two ribosomal RNAs. Additional gene content has been suggested to include microRNAs, piRNA, smithRNAs, repeat associated RNA, long noncoding RNAs, and even additional proteins or peptides (Rackham *et al* 2011; Duarte *et al* 2014; Lee *et al* 2015; Cobb *et al* 2016). The mitochondrial genome requires nuclear-encoded mitochondrially targeted proteins, *e.g.*, TFAM, for its maintenance and expression (Rackham *et al* 2012). The nuclear and the mitochondrial genomes encode peptides of the membrane spanning redox pumps (CI, CIII and CIV) and F_1F_0-ATPase, leading to strong constraints in the coevolution of both genomes (Blier *et al* 2001).

Mitochondrial respiratory control and regulation

The terms metabolic *control* and *regulation* are frequently used synonymously, but are distinguished in metabolic control analysis: “We could understand the regulation as the

mechanism that occurs when a system maintains some variable constant over time, in spite of fluctuations in external conditions (homeostasis of the internal state). On the other hand, metabolic control is the power to change the state of the metabolism in response to an external signal" (Fell 1997). Respiratory control may be induced by experimental control signals that exert an influence on: (*1*) ATP demand and ADP phosphorylation-rate; (*2*) fuel substrate composition, pathway competition; (*3*) available amounts of substrates and O_2, *e.g.*, starvation and hypoxia; (*4*) the protonmotive force, redox states, flux–force relationships, coupling and efficiency; (*5*) Ca^{2+} and other ions including H^+; (*6*) inhibitors, *e.g.*, nitric oxide or intermediary metabolites such as oxaloacetate; (*7*) signalling pathways and regulatory proteins, *e.g.,* insulin resistance, transcription factor hypoxia inducible factor 1.

Mechanisms of respiratory control and regulation include adjustments of: (*1*) enzyme activities by allosteric mechanisms and phosphorylation; (*2*) enzyme content, concentrations of cofactors and conserved moieties such as adenylates, nicotinamide adenine dinucleotide [NAD^+/NADH], coenzyme Q, cytochrome *c*; (*3*) metabolic channeling by supercomplexes; and *(4)* mitochondrial density (enzyme concentrations) and morphology (membrane area, cristae folding, fission and fusion). Mitochondria are targeted directly by hormones, *e.g.*, progesterone and glucacorticoids, which affect their energy metabolism (Lee *et al* 2013; Dai *et al* 2013; Gerö and Szabo 2016; Price and Dai 2016; Moreno *et al* 2017; Singh *et al* 2018). Evolutionary or acquired differences in the genetic and epigenetic basis of mitochondrial function (or dysfunction) between individuals; age; biological sex, and hormone concentrations; life style including exercise and nutrition; and environmental issues including thermal, atmospheric, toxic and pharmacological factors, exert an influence on all control mechanisms listed above. For reviews, see Brown 1992; Gnaiger 1993; 2001; 2009; 2020; Paradies *et al* 2014; Morrow *et al* 2017.

Lack of control by a metabolic pathway, *e.g.,* phosphorylation-pathway, means that there will be no response to a variable activating it, *e.g.,* [ADP]. The reverse, however, is not true as the absence of a response to [ADP] does not exclude the phosphorylation-pathway from having some degree of control. The degree of control of a component of the OXPHOS-pathway on an output variable, such as O_2 flux, will in general be different from the degree of control on other outputs, such as phosphorylation-flux or proton leak flux. Therefore, it is necessary to be specific as to which input and output are under consideration (Fell 1997).

Respiratory control refers to the ability of mitochondria to adjust O_2 flux in response to external control signals by engaging various mechanisms of control and regulation. Respiratory control is monitored in a mitochondrial preparation under conditions defined as respiratory states, preferentially under near-physiological conditions of temperature, pH, and medium ionic composition, to generate data of higher biological relevance. When phosphorylation of ADP to ATP is stimulated or depressed, an increase or decrease is observed in electron transfer measured as O_2 flux in respiratory coupling states of intact mitochondria ('controlled states' in the classical terminology of bioenergetics). Alternatively, coupling of electron transfer with phosphorylation is diminished by uncouplers. The corresponding coupling control state is characterized by a high respiratory rate without control by P» (noncoupled or 'uncontrolled state').

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Author contributions: This manuscript developed as an open invitation to scientists and students to join as coauthors in the bottom-up spirit of COST, based on a first draft written by the corresponding author, who integrated coauthor contributions in a sequence of Open Access versions. Coauthors contributed to the scope and quality of the manuscript, may have focused on a particular section, and are listed in alphabetical order. Coauthors confirm that they have read the final manuscript and agree to implement the recommendations into future manuscripts, presentations and teaching materials.

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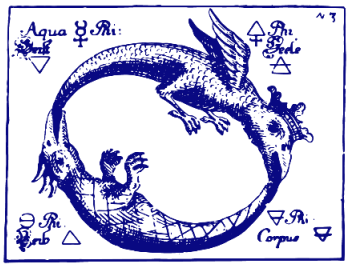

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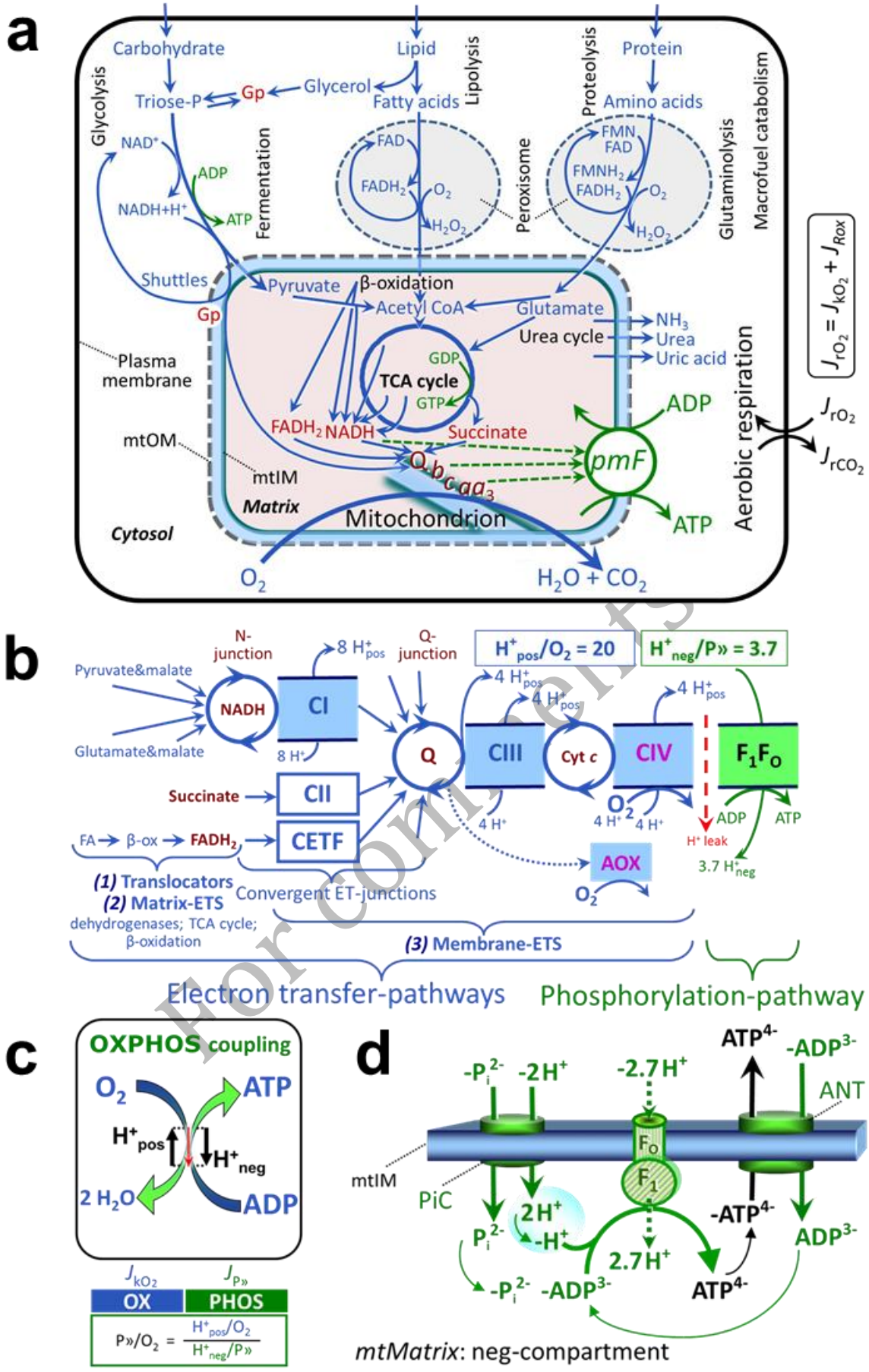

Figure 1.

Figure 1. Cell respiration and oxidative phosphorylation (OXPHOS)
Mitochondrial respiration is the oxidation of fuel substrates (electron donors) with electron transfer to O_2 as the electron acceptor. For explanation of symbols see also **Overview**.

(a) Respiration of living cells: Extramitochondrial catabolism of macrofuels and uptake of small molecules by the cell provide the mitochondrial fuel substrates. Dashed arrows indicate the connection between the redox proton pumps (respiratory Complexes CI, CIII and CIV) and the transmembrane protonmotive force, *pmF*. Coenzyme Q (Q) and the cytochromes *b*, *c*, and aa_3 are redox systems of the mitochondrial inner membrane, mtIM. Glycerol-3-phosphate, Gp.

(b) Respiration in mitochondrial preparations: The mitochondrial electron transfer system (ETS) is (*1*) fuelled by diffusion and transport of substrates across the mtOM and mtIM, and in addition consists of the (*2*) matrix-ETS, and (*3*) membrane-ETS. Electron transfer converges at the N-junction, and from CI, CII and electron transferring flavoprotein complex (CETF) at the Q-junction. Unlabeled arrows converging at the Q-junction indicate additional ETS-sections with electron entry into Q through glycerophosphate dehydrogenase, dihydroorotate dehydrogenase, proline dehydrogenase, choline dehydrogenase, and sulfide-ubiquinone oxidoreductase. The dotted arrow indicates the branched pathway of oxygen consumption by alternative quinol oxidase (AOX). ET-pathways are coupled to the phosphorylation-pathway. The H^+_{pos}/O_2 ratio is the outward proton flux from the matrix space to the positively (pos) charged vesicular compartment, divided by catabolic O_2 flux in the NADH-pathway. The H^+_{neg}/P» ratio is the inward proton flux from the inter-membrane space to the negatively (neg) charged matrix space, divided by the flux of phosphorylation of ADP to ATP. These stoichiometries are not fixed because of ion leaks and proton slip. Modified from Lemieux *et al* (2017) and Rich (2013).

(c) OXPHOS-coupling: The H^+ circuit couples O_2 flux through the catabolic ET-pathway, J_{kO_2}, to flux through the phosphorylation-pathway of ADP to ATP, $J_{P»}$.

(d) Phosphorylation-pathway catalyzed by the proton pump F_1F_O-ATPase (ATP synthase), adenine nucleotide translocase (ANT), and inorganic phosphate carrier (PiC). The H^+_{neg}/P» stoichiometry is the sum of the coupling stoichiometry in the F_1F_O-ATPase reaction (-2.7 H^+_{pos} from the positive intermembrane space, 2.7 H^+_{neg} to the matrix, *i.e.*, the negative compartment) and the proton balance in the translocation of ADP^{3-}, ATP^{4-} and P_i^{2-} (negative for substrates). Modified from Gnaiger (2020).