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Redox Signaling

Mitochondria is best known as the powerhouse of the cell, also known for its production of ATP (adenosine triphosphate) through cellular respiration. But often overlooked or not thought of in the sense of being a cell regulator. But truth is the mitochondria plays a big role in regulating the cell in which it allows for cell proliferation, slowing down of cell proliferation, and apoptosis. Depending on the functional state of the mitochondria it produces signaling molecules such as ROS(reductive oxygen species) which determine the fate of the cell such as proliferation, differentiation, or apoptosis. It is important to note that the mitochondria do not intend to regulate the cell like a thinking entity, but regulation is possible due to biochemical and mechanical activities they control, and influence therefore governed by the law of thermodynamics and physics which facilitate the production of ROS.

ROS, or reactive oxygen species, are harmful by-products of mitochondrial metabolism but also key to cell regulation. ROS includes superoxide anion, Hydrogen Peroxide, Hydroxyl radical. It is important to note that ROS are highly reactive partly due to oxygen's electronegativity but is mostly due to the reason that many ROS contain an unpaired electron (free radicals), making them unstable free radicals. Because they seek to gain electrons and reach a more stable state, ROS will oxidize nearby proteins, DNA, and lipids depending on the specific species involved and is why they are harmful in some cases. ROS as said before is a by-product of mitochondrial metabolism specifically due to the Electron transport chain (ETC) in which complex I leaks electrons due to reasons such as ETC backed up or NADH levels high or ATP synthase not working fast enough in which Oxygen accepts leaked electrons because it is highly electronegative and because it is the final electron acceptor of the ETC. This superoxide anion is then transformed into H_2O_2 by superoxide dismutase and then when in the presence of a metal such as Fe^{2+} and given the right conditions (peroxidase being overwhelmed) can be converted into hydroxyl radicals. So, oxygen is the starting point (the base) for the entire ROS pathway.

While harmful ROS can indirectly allow pathways such as Akt, ERK, JNK, p38 MAPK, p53, and others mentioned in the reading. ROS does this through the modification of redox-sensitive regulatory proteins rather than directly activating or deactivating kinases it also does this through the activation/inactivate phosphatases, which indirectly leads to kinase activation. One example of ROS indirectly allowing for inactivation of a phosphatase is Akt pathway. In which low levels of

ROS allows for oxidation of PTEN (cysteine) → PTEN inactivated → PIP3 is not converted to PIP2→PIP3 accumulates at the membrane→ Akt recruited to the membrane PDK1 + mTORC2 phosphorylate Akt→ Akt activated. Most of the pathways follow a similar principle. The only difference is that ROS indirectly activates/deactivates kinases or phosphatases by modifying redox-sensitive kinases or phosphatases. It is important to note that pathways such Akt, ERK allow for cell proliferation and pathways such as JNK and p38 MAPK slow down cell proliferation while p53 allows for apoptosis while at the same time acting as a checkpoint that if passed gives way to cell proliferation. These pathways and their activation is largely determined by ROS concentration, showing the major role of ROS as concentration dependent signaling molecules.

For example, ROS at low concentration acts in the Regulation of Cellular Processes, Redox Signaling. Specifically at low levels around 10^{-11} to 10^{-12} M—H_2O_2 promotes cell growth. low concentrations activate ERK1/2, Phosphorylation of kinases as ERK1/2 and protein kinase B (Akt) 1 and 2 depends on the presence of their upstream kinases mitogen protein kinase 1 and 2 (MEK1/2) and PI-3K-dependent kinase 1 (PDK1) this in turn allows for the expression of Cyclin D1 and pushes the cell from G1 into S phase. Tumor cells often maintain this low-ROS environment by decreasing their mitochondrial respiratory rate, a metabolic shift like the Warburg effect. This reduces ROS production enough to keep ERK active and allow uncontrolled proliferation. In this way, mitochondria regulate growth not just by generating ATP, but also by tuning redox signals that turn on pro-growth pathways

A modest increase in ROS can elevate p53 levels, which promotes activation of proliferative kinases such as Akt and ERK1/2, supporting cell growth and proliferation. It is important to note that p53 does not activate proliferative kinases. Instead, it acts as a checkpoint regulator that inhibits cyclin-CDK activity, promotes DNA repair, or induces apoptosis depending on stress level. However, this slightly higher ROS often seen during differentiation can activate stress-related kinases such as JNK and p38 MAPK. These pathways encourage cells to slow proliferation and begin specialized functions. This redox-dependent switch between ERK (growth) and JNK/p38 (stress or differentiation) demonstrates how mitochondria influence the balance between cell cycle progression and cell cycle arrest.

When cells reach a high level of ROS and an increase of activity in ETC it leads to a decrease in AKT and ERK1/2 and an increase of P53. This increase of ROS also leads to an increase of activation of proapoptotic kinases, such as c-Jun-NH2- terminal kinase (JNK) and p38 mitogen-activated protein kinase (MAPK). Conversely, differential activation of JNK and p38 MAPK conducts cell differentiation and finally to cell cycle arrest and apoptosis. ROS, while potentially damaging, are critical signaling molecules that regulate cell growth, differentiation, and death through complex redox-sensitive pathways involving kinases like ERK, Akt, JNK, p38, and tumor suppressors like p53. Mitochondria play a central role in balancing these ROS signals to control cell fate decisions. ROS also plays roles in other parts of the cell such as allowing proteins to fold in the rough ER or in an immune cell where the phagosome enzyme NADPH oxidase and SOD and it allows for the creation of HOCl (essential bleach) which allows for the disintegration of bacteria

At low concentration ROS promotes cell growth as ROS levels rise it triggers stress response that slow proliferation and at high concentrations, they initiate apoptosis. This complex system shows how ROS embodies a paradox in which molecules born of oxygen's reactive power that can both threaten life and sustain it. Their dual nature reminds us that balance is fundamental in biology. Just as a flame can warm or burn, ROS wield destructive potential and essential signaling capacity. It is in this delicate equilibrium the fine tuning between damage and signaling that life finds resilience and adaptability, continuously negotiating survival through change. This also reflects the complexity of human life and the beauty in complex living systems. Ultimately, like all matter and energy, we too move toward a state of maximum entropy, a final equilibrium reminding us of the gift given to us by Mother Nature which is to be and think.