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A new mitochondrial theory of ageing subsumes apoptosis

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ABSTRACT: This new Mitochondria theory of ageing encapsulates most of the previous theories on ageing. The explosion of knowledge available from the Molecular Biology of Mitochondria biogenesis furnished an avalanche of Biochemical information, including the location of the long-souight-for,LONGEVITY GENE, which is now located in the Mitochondria. This recent discovery singles out mitochondrion as a BIOMARKER OF AGEING.

'New Mitochodrial Theory of Ageing' is pivoted on Mitochondrial Molecular Biology and Biochemistry particularly as they relate to mitochondrial biogenesis. The highpoint of the theory revolves around the roles of "Mitochondrial genome" as well as the in-situ production of "mitochondrial free radicals" in proportion to ingested calories from diets which precipitate such damages afflicting the genome(DNA and RNAS) primarily and other molecules secondarily resulting in molecular mayhem and gradual functional dysfunctions which culminate in ageing.

Apoptotic proteins results from error-laden mitochondrial genomics and proteomics Wyllie(1972) correctly observed and described "apoptosis" which is the down-stream" of this new mitochondrial theory of ageing .Recent advances in Molecular Biology of Mitochondria revealed the whole "gamut"of processes in ageing. It culminated in the discovery of "longevity gene" in 2003. Hence, this new mitochondrial theory of ageing subsumes apoptosis-whereas apoptosis itself was the tip of the ice-berg of cell-death. Therefore, this new mitochondrial theory of ageing, is the whole iceberg on ageing, and thus a new mitochondrial theory hereby postulated and described in details.

Key Words: Mitochondrial Theory; Ageing; Longevity; Apoptosis; Biogenesis; Genomics.

A INTRODUCTION

Wyllie (1) while studying tissues with electron microscopes discovered APOPTOSIS. Apoptosis is a process of deliberate life relinquishment by a cell in a multicellular organism. Etymologically ,Apoptosis is derived from Greek: apo "from" ptosis "falling",It involves an orchestrated of biochemical events leading to a characteristic cell morphology and death. Research on apoptosis has increased substantially since early 1990s

The explosion in the molecular biology of mitochondrial biogenesis which Wyllie was not privy to has informed this new theory. Guarante and Mason (2) 1983 reported a radical departure as a result of MOLECULAR BIOLOGY EXPLOSION in Yeast Mitochondrial studies. The mitochondria are essential to multicellular life, without them a cell ceases to respire aerobically and quickly dies-a fact exploited by some apoptotic pathways, However, apoptotic proteins which target mitochondrial affect them in different ways ;they may cause mitochondrial swelling through the formation of membrane pores or they may increase the permeability of the mitochondrial membrane and cause apoptotic effectors to leak out Cotron *et al* (3).

The process of apoptosis is controlled by a diverse range of cell signals which may originate extracellularly or intracellularly. Extracellular signals may include hormones, growth factors, nitric oxide or cyctokines and therefore must either cross the plasma membrane or transducer to effect a response Bruine (4)

In view of the discovery of the longevity gene which now is known to be located on the mitochondria and also sex-linked [Attardi (5)];the erstwhile apoptotic programmed-cell death processes are merely "down-stream processes" of a whole gamut of processes leading to a broader control of life and life-processes by the newly discovered "longevity-gene, located on the mitochondria, no doubt ,Wyllie (1972) saw an aspect of Mitochondrial roles of programmed cell death which he called apoptosis; but Attardi (2003) reported that the Longevity Gene (in the mitochondria) has the overall responsibility for all cell processes culminating in death which "Apoptosis" euphemistically referred to as deliberate life relinquishment by a cell in a multicellular organism

Finally it is pertinent to recall that mitochondrion is the only organelle that is essentially membranous with its own separate genome and protein synthetic apparatus –apart from the nucleus. Mitochondrial imperfect electron transport produces free radicals in-vivo in direct proportion to the ingested calories through diets. Indeed, mitochondrion ,is now known to house the Longevity gene. Recent advances in Molecular Biology and Biochemistry have implicated mitochondrial with "free radical stress" Degenerative diseases of the Aged and "Ageing". All the above have led this author to postulate the "NEW MITOCHONDRIAL THEORY OF AGEING" which naturally and convincingly subsumes APOPTOTIC PROGRAMMED CELL-DEATH OF WYLLIE(1972)

The organelle mitochondrion is a specialised one for respiration and oxidative phosphorylation (6).The organelle also performs many other important functions. It has been documented (7) that mitochondria synthesize heme, lipids, amino-acids and nucleotides as well as mediating the intracellular homeostatis of inorganic ions. Although respiration and ATP-synthesis are two main functions of mitochondria but ;under anaerobic conditions these functions may just be a tip of the iceberg relative to the totality of metabolic functions of the cell which the organelles mitochondria mediate (8). In summary, it is now known that mitochondria are essential organelles which cannot be lost from the cell without the loss of cell viability Hence, for eukaryotes, "No mitochondrion, no cell"(9)

There is absolutely no doubting the fact that after the nucleus ,the mitochondrion is next ,considering essentiality for life, for they alone possess the self-replicating molecules. Deoxyribonucleic acids (DNA) which contains the blue-prints for life. Mitochondrial biogenesis is a serious molecular business It involves the flow of molecules into and out of mitochondria. Extensive work (10-15) have shown that there are coordinating signals between the mitochondrial genome and the molecular genome.

Evolution theory indicates that ageing is caused by progressive accumulation of defects since the evolutionary optimal level of maintenance is always below the minimum required for indefinite survival. Most of the theories of ageing also suggest that multiple processes are operating in parallel but unfortunately they make no predictions about specific mechanisms To understand this new theory of ageing which encapsulates all the major previous theories ,particularly (a) the genome-based theory (b) the calorie restrictions theory(c) the free radical theory and (d) the catastrophe theory of Orgel. This new theory implicates the organelle MITOCHONDRION, as its pivot as well as the BIO-MARKER organelle for ageing phenomenon. The theory is a fall-out of recent advances in Biochemistry and Molecular Biology. The new "MITOCHONDRIAL THEORY OF AGEING clearly explains mechanistically, how the cell crashes under the yoke of molecular dysfunctions, which culminate to, and manifest themselves as, burden of AGEING.

B DESCRIPTION OF "NEW MITOCHONDRIAL THEORY OF AGEING"

The crux of the New Mitochondrial theory of Ageing is its genome. This unique property of mitochondrion (as a cellular organelle)is that it has its own DNA (deoxyribonucleic acid).When DNA is wrapped in histones a form of storage ptoteins, it becomes chromosomes. Mithochondrial DNA lacks histones they are different from nuclear DNA in several respects viz:

(1) It exists as a simple plasmic (a DNA loop) and in this respect it is more akin to bacterial DNA than the chromosomal DNA of higher organisms
(2) Mt DNA is not associated with histones hence they are unprotected literally

(3) Most of the complex DNA repair mechanisms that correct damages to nuclear DNA are absent from mitochondria
(4) Mitochondrial transcriptional and translational processes are located together inside the mitochondrion-unlike the nucleo-cytoplasmic arrangement of the nuclear genome

It is a fact that the relatively unprotected and unrepaired and DNA suffers more than ten times the damage experienced by the nuclear DNA (16) These damages give rise to DNA-mutation hypothesis of cell ageing(17)It also explains the Orgels catastrophic theory which was proposed in 1968 to account for the accumulated genomic errors resulting from random errors in translation and transcription during DNA-replication.The error theory asserted that frequent errors in DNA replication will produce imperfect mRNA molecules which may lead to faulty enzymes. The Orgel theory concludes that ageing proceeds at the same rate as the accumulation of genomic errors.

Mitochondrial Theory of ageing encompasses all the genome-based theories. Be it the Somatic Mutation theory or redundant theory of Ageing. Mitichondrial electrons transport is not perfect even under ideal conditions some electrons "leak" from the electron transport chain. These leaking electrons interact with oxygen to produce superoxide radicals. With mitochondrial "ageing" and dysfunction ,leakage of electrons can increase significantly. At senescence mitochondria behave rather differently. The close proximity of mtDNA to the flux of superoxide radicals (or hydroxyl radicals) coupled with its unproteceted DNA lacking repair mechanisms, lead to free-radicals mediated mutations and deletions precipitating ageing symptoms and diseases

Mitochondrial Theory of Ageing has been proposed as a fundamental underlying cause of (a) Free radical stress (b)Degenerative diseases and (c) Ageing .The fact that mitochondrial dysfunction has been linked to various pathologies associated with ageing is in support of this new theory of Ageing. lndeed, mitochondrial defects have been identified in Parkinson's disease, Alzheimer's disease, Heart disease, Fatigue syndromes, numerous genetic conditions and nucleoside therapy of AIDS. Indeed reduction in dietary calories favours longevity. This calories restriction theory is also explained by the new Mitochondrial Theory of Ageing. More calories more free radicals rapid ageing. Less calories less free radicals slow ageing and longer life. Dietary calories affect mitochondrial integrity and longevity.

C. EXPERIMENTALS SUPPORT FOR THE "MITOCHONDRIAL THEORY OF AGEING"

Experiment 1:

We reported in 1986 (130) on the peculiarities of proteins and RNA syntheses in the hepatic mitochondria of *young* and *old* rats . The abstracts of the work reported in "*Experimental Gerontology*" in 1988 is hereby reproduced in support of this theory. "Pulse –labelling in the presence of antibiotics is so widely used in mitochondrio-genesis that the shortcomings of the method is usually overlooked (18-21). In this paper, we present the results of experiments on the biogenesis of mitochondria done without the use of antibiotics. The method of kitagawa and sugimoto (22) for the estimation of in-vivo translational activity of rat liver mitochondrial without the use of antibiotics was employed. The syntheses of RNA and protein in rat liver mitochondria of young and old rats was investigated. Incorporation of ^{14}C-ATP into the RNA of isolated mitochondria occurs at the same level in both young and old rats. However, the incorporation of 14C-leucine into the two fraction of mitochondria , i.e mitochondria protein of nucleo-cytoplasmic origin and those of intrinsic mitochondria origin are at the same level of young rats. In old rat , incorporation of the tracer into mitochondria origin (which is at the same level as that of young rats) is three times greater than the incorporation of the tracer into mitochondrial protein of nucleo-cytoplasmic origin. These findings suggest that the role of the mitochondrial genome in the biogenesis of mitochondria increases at senescence and that the synthesis of corresponding regulatory proteins which are of nucleo-cytoplasmic origin decreases at senescence".

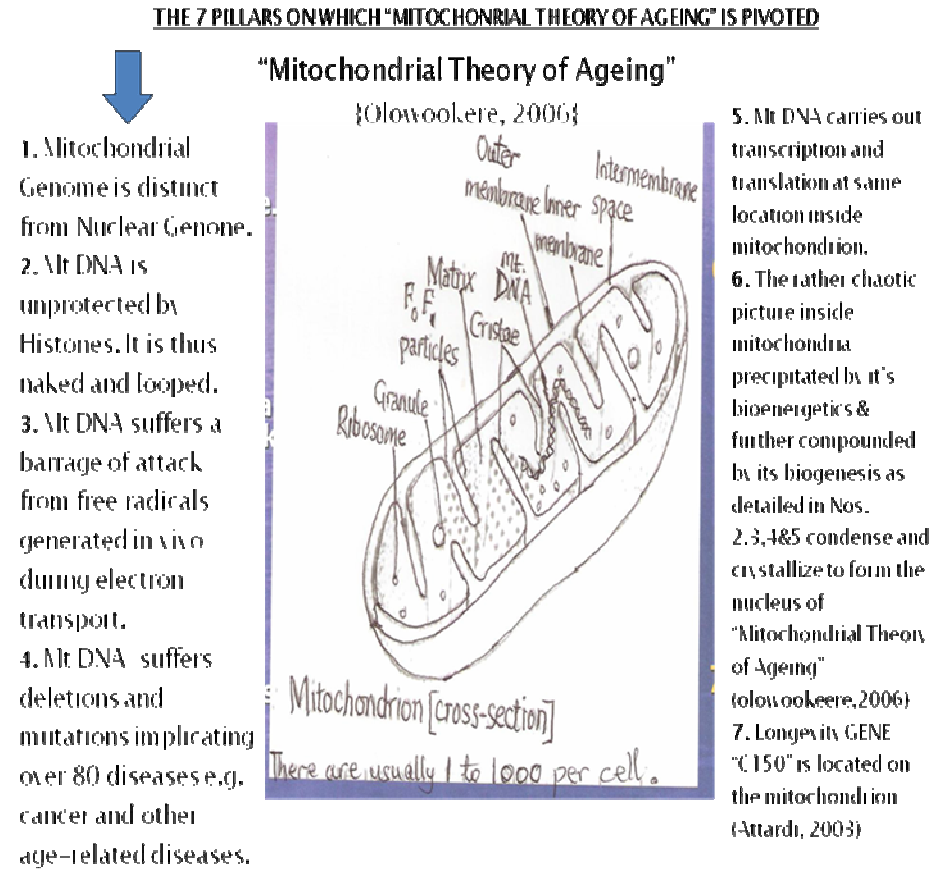

Fig 1: showing a cross-section of mitochondrion ,lucidly illustrates this MITOCHONDRIAL THORY OF AGEING which is pivoted on seven Biochemical and molecular Biology contemporary facts strategically positioned around the T/S of the organelle MITOCHONDRION carrying the process of AGEING on its head the way ATLAS carries the world on its head

Experiment 2:

Olowookere *et al*. (23) reported in the journal of comparative physiology B that different dietary levels (represented by kwashiorkor and obesity) affect mitochondrial respiration as well as resting metabolic rates of rats. The summary of the work is hereby reproduced in support of the "New Mitochondrial Theory of Ageing " vis-à-vis dietary calories and general metabolism in animal models; "Resting metabolic rates have been measured and compared with hepatic mitochondrial respiration in kwashiorkor and diet-induced obese weaned rats. In kwashiorkor , resting metabolic rate was 21% lower than the value of controls, while that of obese rats was 14% higher than in control animals. The resting metabolic rate for kwashiorkor animals was 50% of the predicted basal metabolic rate (BMR), whereas, that of the obese was 23% higher than the predicted BMR". The mitochondria oxygen consumption pattern , using malate plus glutamate or succinate as respiratory substrates, revealed that the resting respiration (state 4) was 23.9% higher in kwashiorkor and 29.1% higher in obese animals . Whereas , the active (state 3) respiration was 34.8% lower in kwashiorkor and 43.3% lower in obese rats compared to controls. The respiratory control ratios(RCR) were 51.1% and 43.8% in kwashiorkor and obese rats , respectively, relative to the values in controlrats. It is concluded from this study that kwashiorkor syndrome and Diet-induced obesity interfere with oxygen utilization at the level of state 3 mitochondrial respiration , which are markedly decreased when compared to the values of control animals" Invariably, obese animals mitochondria generate more free-radicals than kwashiorkor animals` mitochondria. Obesity is thus inimical to ageing process while kwashiorkor aids longevity. Indeed

"Calories restriction theory of ageing" also came to the same conclusion from different perspectives . Hence , the "New Mitochondria Theory of Ageing" explains and encapsulates (1)free-radical theory (2) Genome-based theory (3) Calories restriction theory of ageing (4) Integrated theories of Ageing and (5) Orgel`s errors` theory of Ageing which stem from the bombardment of DNA and RNAS leading to the corruption of the "fidelity of protein synthesis"!

D. CONCLUSION

This new theory of Ageing viz; **"MITOCHONDRAL THEORY OF AGEING"** has been made possible by the recent advances in **MOLECULAR BIOLOGY**. Recent advances in the biochemistry and Molecular Biology of the mitochondrion as well as the genomics of this vital organelle which furnishes information that make the new theory possible.
Biogenesis of mitochondria which became clearer from Molecular Biology perspectives , **X**-rayed the protein synthetic machinery of the mitochondrion as well as its proteomics. Apoptotic proteins result from error-laden mitochondrial genomics and proteomics! The closeness of both the translational processes as well as the attendant problem of such "jam-packing" of sensitivity processes further facilitate and enabled the author to package this new theory. A functional theory that explain s why the cell crashes under the burden of genomics errors and proteomics dysfunctions epitomized inside the mitochondrion. Unlike the apoptotic programmed cell –death ,it is not spontaneous , rather long-encoded in the Longevity Gene "C150T" in the mitochondria (24) .This new theory adds a new feather to the crown of the organelle mitochondrion which essentially and solely controls Biological Energy Transduction as well as significantly contributing to our present knowledge and understanding of the **"BIOLOGY OF AGEING"**

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