# Cutting edge and hypotheses on L-Proline mitochondrial metabolism and autophagy: novel prospective and possible therapeutics in COVID-19 Pandemic era (i.e. 33 years at lab)

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**Abstract:**
Research over the last decade has extended the prevailing view of cell mitochondrial function well beyondits bioenergetic role in supplying ATP, recognizing that the mitochondria play a critical role in the responsesof cells to metabolic transition and physiological stresses. Previous studies on wild-type Saccharomycescerevisiae ATCC 18790 and two strains found in grape showed the capability of yeast mitochondria to takeup and oxidise L-Proline externally added them. L-Proline caused mitochondrial membrane potential (Δ)generation with a rate proved to depend on the transport across the mitochondrial membrane as wasshown by means of inhibitors N-ethylmaleimide and bathophenanthroline and others.The dependence ofthe rate of generation of Δ on the increasing L-Proline concentrations exhibits hyperbolic kinetics. Differently from mammalians and plants, as a results of L-Proline addition, in physiological conditions, theappearance of Glutamate was not found outside yeast mitochondria as measured by HPLC experiments andby GDH detecting system. Proline mitochondrial metabolism in the response to metabolic transition respectto environmental " feast" and "famine" conditions was, also, debated in Pallotta 2005.The stressful ecosystems exert strong adaptive pressure and proteins that facilitate these adaptationprocesses are candidate drug targets. Nucleotides are the core of biochemical pathway required for cancercell growth and replication and genetic changes will lead in oscillation in their pools. Although it isquestionable whether the Warburg effect actually causes cancer, impairing D-glucose uptake andmetabolism induces oxidative metabolism.L-proline homeostasis is critical in a constellation of human diseases, in parametabolic linkage betweencancer, epigenetics and bioenergetics (Pallotta 2013,2014,2016) where degradation and biosynthesis arerobustly affected by oncogenes or suppressor genes that can modulate intermediates involved inepigenetic regulation. L-Proline-fueled mitochondrial metabolism involves the oxidative conversion to LGlutamate by a flavin dependent-L-Proline Dehydrogenase/Oxidase and a NAD+ -dependent L-Δ1 -Pyrroline-5-carboxylate Dehydrogenase. In Saccharomyces cerevisiae, an important test tube, Put1p andPut2p respectively help cells to respond to changes in the nutritional microenvironment by initiating LProline breakdown after mitochondrial uptake (Pallotta 20013,2014). In this preclinical research,lowmolecular weight compounds were tested for inhibiting L-Proline mitochondrial transport and Put1p/Put2pcatalytic activities. Thus, in seeking for natural bioactive compounds targeting L-Proline pathway and its-

substrate channeling (Becker's group 2018), e reported data using in silico screening and in vitro studies inSaccharomyces cerevisiae with genetic background ATCC18790 but different phenotypic landscape inducedby nutritional stress/pH changes (Pallotta 2016). Cells vitality, Δ measurements, NAD(P)+ /NAD(P)H pooland flavine turnover were determined in spectrofluorimeter microplater reader and via HPLC (Pallotta et al 1998, 1999,2004; Pallotta2011; Di Martino Pallotta2011) thus in supporting of future disease therapies with decreasing side effects. Multiple studies have also shown a crosstalk between ER stress and autophagy. When ER stress occurs, autophagy can be triggered by unfolded protein reactions (UPR) to remove excessive unfolded proteins and damaged organelles, and maintain cell homeostasis.

**Biography:**

Biochemist/Biophysicist, Principal Investigator- Department of Medicine and Health Sciences- University of Molise ITALY Meeting with joined sessions GIBB (Italian Group of Bioenergetics and Biomembranes)-Membrane and Bioenergetic Group of SIB (Italian Sociaty of Biochemistry), Italy, June 1997.From research to calendar Multiple Sclerosis 2015-2020 May 2015 CB, ItalyMembership in scientific societies:SIB (Italian Sociaty of Biochemistry)and Italian Group of Bioenergetics and Biomembranes (since 1999);Women in Science; EUSTM (European Society for Translational Medicine), ISM (International Society of Microbiota) Member of the council of PhD in Applied Biochemistry and Chemistry, University of Molise (from 2003 to2005) .Member of the council of PhD in Health Science, University of Molise (since 2005).

**Recent Publications:**

1. Pallotta ML The role of proline uptake in yeast mitochondria and the feast-famine regime. Yeast, Vol.22

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