



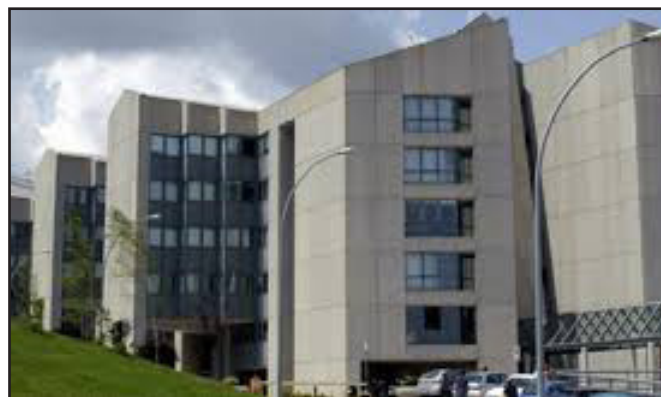
Cutting edge and hypotheses on L-Proline mitochondrial metabolism and autophagy: novel prospective and possible therapeutics in COVID-19 Pandemic era (i.e. 33 years at lab)

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Abstract:

Research over the last decade has extended the prevailing view of cell mitochondrial function well beyond its bioenergetic role in supplying ATP, recognizing that the mitochondria play a critical role in the responses of cells to metabolic transition and physiological stresses. Previous studies on wild-type *Saccharomyces cerevisiae* ATCC 18790 and two strains found in grape showed the capability of yeast mitochondria to take up and oxidise L-Proline externally added them. L-Proline caused mitochondrial membrane potential ($\Delta\psi$) generation with a rate proved to depend on the transport across the mitochondrial membrane as was shown by means of inhibitors N-ethylmaleimide and bathophenanthroline and others. The dependence of the rate of generation of $\Delta\psi$ on the increasing L-Proline concentrations exhibits hyperbolic kinetics. Differently from mammals and plants, as a result of L-Proline addition, in physiological conditions, the appearance of Glutamate was not found outside yeast mitochondria as measured by HPLC experiments and by GDH detecting system. Proline mitochondrial metabolism in the response to metabolic transition respect to environmental “feast” and “famine” conditions was, also, debated in Pallotta 2005. The stressful ecosystems exert strong adaptive pressure and proteins that facilitate these adaptation processes are candidate drug targets. Nucleotides are the core of biochemical pathway required for cancer cell growth and replication and genetic changes will lead in oscillation in their pools. Although it is questionable whether the Warburg effect actually causes cancer, impairing D-glucose uptake and metabolism induces oxidative metabolism. L-proline homeostasis is critical in a constellation of human diseases, in parametabolic linkage between cancer, epigenetics and bioenergetics (Pallotta 2013, 2014, 2016) where degradation and biosynthesis are robustly affected by oncogenes or suppressor genes that can modulate intermediates involved in epigenetic regulation. L-Proline-fueled mitochondrial metabolism involves the oxidative conversion to L-Glutamate by a flavin dependent L-Proline Dehydrogenase/Oxidase and a NAD⁺-dependent L- Δ^1 -Pyrroline-5-carboxylate Dehydrogenase. In *Saccharomyces cerevisiae*, an important test tube, Put1p and Put2p respectively help cells to respond to changes in the nutritional microenvironment by initiating L-Proline breakdown after mitochondrial uptake (Pallotta 2001, 2013, 2014). In this preclinical research, low molecular weight compounds were tested for inhibiting L-Proline mitochondrial transport and Put1p/Put2p catalytic activities. Thus, in seeking for natural bioactive compounds targeting L-Proline pathway and its



substrate channeling (Becker's group 2018), we reported data using *in silico* screening and *in vitro* studies in *Saccharomyces cerevisiae* with genetic background ATCC18790 but different phenotypic landscape induced by nutritional stress/pH changes (Pallotta 2016). Cells vitality, $\Delta\psi$ measurements, NAD(P)⁺/NAD(P)H pool and flavine turnover were determined in spectrofluorimeter microplate reader and via HPLC (Pallotta et al 1998, 1999, 2004; Pallotta 2011; Di Martino Pallotta 2011) 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 Society of Biochemistry), Italy, June 1997. From research to calendar Multiple Sclerosis 2015-2020 May 2015 CB, Italy Membership in scientific societies: SIB (Italian Society 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 to 2005). 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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