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After his PhD, obtained in 2003 at the medical school of Montpellier University, Dr. Jérémy Fauconnier joined the Muscle Physiology group of Pr. H. Westerblad at the Karolinska Institute (Stockholm, Sweden). After two years of postdoctoral research and following three years as a fellow of the National Institute for Medical and Health Research (France), Dr. Jérémy Fauconnier was recruited as a permanent researcher by the French national center for scientific research (CNRS) at Montpellier University. Dr. Jérémy Fauconnier, as a specialist in cellular electrophysiology and calcium imaging has published numbers of originals and review articles focusing on Calcium signaling, excitation-contraction coupling and mitochondrial function. His contribution to the scientific community goes far beyond his research activities. He built up the national Young Investigator Group for Basic Cardiovascular Research with the aim to support scientific, educational, and advocacy activities of the French Society of Cardiology (GRRC/SFC). He is also a founding nucleus member of the Scientist of Tomorrow of the European Society of Cardiology and he belongs to several national and international scientific councils where he organizes workshop and scientific events dedicated to the Young Research community.

Commentary on 'Cytosolic proteostasis through importing of misfolded proteins into mitochondria' by Ruan *et al.*, *Nature* 2017.[2]

Cellular proteostasis is a fine-tuned system, highly hierarchized, coordinating the balance between protein synthesis and protein degradation. The synthesis of some 20 000 different proteins expressed in mammal cells is initiated on ribosomes as single polypeptides. The newly synthesized polypeptides are subjected to folding processes to acquire their final three dimensional conformations and fulfil their biological functions. Under environmental stress conditions, mutations and/or translational defects, the folding is impacted and misfolded protein intermediates are generated. Fortunately, a highly conserved system of protein quality control, based on chaperones, ensure the refolding or the degradation of such misfolded proteins. Indeed, if the refolding is impossible, the misfolded proteins are degraded and eliminated *via* the ubiquitin-proteasome pathway (UPP) and/or the autophagy process. Under certain pathophysiological conditions, the quality control is overwhelmed, misfolded proteins accumulate and protein aggregates are formed. Although protein aggregates may appear as disorganized structures, some misfolded proteins aggregate as ß-sheets, forming amyloid fibrils. Depending on their subcellular localization, protein aggregates impair cell function, cause cellular toxicity, and promote cell death and mitochondrial dysfunction.

Roughly, the aggregates' compartmentalization and clearance pathways depend on their solubility profile. Soluble aggresomes co-localize either with the microtubule organizing centre or with the juxtanuclear quality control (JUNQ) compartment, therefore, appearing in close vicinity with the endoplasmic reticulum or the nuclear envelope. The insoluble protein deposit compartment, as its name suggests, concentrates non-diffusible misfolded proteins in the cytosol. In this latter case the protein inclusions are eliminated by autophagy, whereas misfolded proteins in the JUNQ compartment are either refolded or degraded by the UPS. Importantly, these pathways are conserved throughout the evolutionary tree from yeast to mammals.[1] In addition to these classical proteostasis pathways, Ruan *et al.*[2] bring another piece to the quality control jigsaw: mitochondria. They identified, in yeast, protein aggregates that clump to the outer membrane of mitochondria and, after a disaggregation process, the proteins are imported in the mitochondrial matrix where they are degraded by mitochondrial proteases.[2] The authors name this novel clearance pathway MAGIC for mitochondria as guardian in cytosol. The magical aspect probably lies in the conservation of this process throughout evolution, as they also observed mitochondrial-mediated protein clearance in a human cell line.

So what is the MAGIC trick? After a heat shock protocol, they observed that protein aggregates were enriched with outer mitochondrial membrane proteins involved in protein import (Tom70 and Tom40), and these aggregates were localized in close vicinity with the

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mitochondrial outer membrane. After an unfolding process, presumably under the control of the chaperone HSP104, proteins are imported in the mitochondria following the classical mitochondrial import pathway. This pathway depends both on the TIM23 complex to pass through the inner membrane and on the mitochondrial electrochemical gradient. Once in the matrix, the LON protease Pim1 cleaves and disaggregates the imported proteins. The contribution of mitochondria to protein quality control raises thousands of questions: does it affect mitochondrial function and mitochondrial respiration capacity? What happens to the amino acids originating from the protein degradation within the mitochondria? Does it compete with classical mitochondrial protein import processes? Does this process influence mitochondrial fusion/fission and mitophagy initiation? Does this process target specific aggregate compositions? And above all, how is this mechanism relevant in pathophysiological conditions and in particular in the cardiovascular system?

In the heart, upon various pathophysiological stresses and in the absence of cell division, the only suitable mechanism to adapt to the workload is to change the size of the cardiomyocytes and the mitochondrial content. On one hand, an extreme activation of the protein quality control process induces a progressive and excessive degradation of proteins, and leads to myolysis and ultimately cardiac failure (i.e. idiopathic dilated or hypertrophic cardiomyopathy, or atrial fibrillation).[3] On the other hand, alterations in the UPP and/or autophagy may result in excessive protein aggregates, as observed in atherosclerosis, in diabetes-mediated cardiovascular defects or desmin-related cardiomyopathies.[3] In these pathologies, mitochondrial dysfunctions such as mitophagy, mitochondrial fusion/fission, or branched-chain amino acids catabolism[4,5] are commonly reported. There is no doubt that a MAGIC box could play a crucial role in the cellular quality control disturbance associated with these myocardial dysfunctions.

In yeast, the MAGIC system requires HSP104 for the mitochondrial uptake of aggregating proteins, but defects in HSP70 also appear to increase the mitochondrial import of misfolded proteins and induce mitochondrial stress.[2] Interestingly, the incidence of post-operative atrial fibrillation is positively correlated with a decrease in Hsp70 expression and function and, on another hand, to mitochondrial dysfunction.[6,7] Similarly, in acute myocardial ischaemia increased Hsp70 expression was reported to limit reperfusion injuries and improve post-ischaemic recovery.[8,9] Of course, it is premature to affirm that HSP70 would impact mitochondrial function through a perturbation of the MAGIC process, but one can still speculate that an increase in the import of protein aggregates in mitochondria associated with HSP70 defects may contribute, at least partly, to the mitochondrial disorders currently observed in the setting of atrial fibrillation or myocardial ischaemia.

Besides chaperones, mitochondrial import of protein aggregates may theoretically impact mitochondrial fate. Indeed, PINK1 (PTEN-induced kinase 1), a kinase involve in the mitophagy initiation, is imported in the mitochondria through the translocase of the outer membrane (TOM)/translocase of the inner membrane (TIM) machinery and cleaved in the mitochondrial matrix by proteases. The cleaved PINK1 is subsequently degraded in the cytosol by the UPS system. Under pathological stress, when the import process is affected, PINK accumulates in the mitochondrial outer membrane and initiates mitophagy. In the study of Ruan *et al.*,[2] mitophagy has not been investigated but it would be interesting to determine whether MAGIC competes with the PINK1 cycle, particularly in the context of atherosclerosis in which autophagy/mitophagy becomes dysfunctional with plaque progression and rupture.[10]

More generally, both mitochondrial and proteostasis defects pave the way to cardiovascular senescence and ageing.[3,10,11] Compiling evidence indicate that preservation of the protein quality control would delay the cardiovascular senescence and prolong lifespan. Pharmacological modulation of proteostasis has thus become over the last decade a therapeutic issue, not only in neurodegenerative disease but also in cardiovascular diseases.[3,10] In this context, Ruan *et al.* open a new field of interest where waving a MAGIC wand might be a novel therapeutic strategy to prevent myocardial senescence and pathological ageing.

Conflict of interest: none declared.

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