Leducq Network

Modulating Autophagy to Treat Cardiovascular Disease

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The Fondation Leducq, created by the French entrepreneur Jean Leducq and his wife Sylviane, supports international collaborative research to combat cardiovascular disease (CVD) and neurovascular disease. Our Network, Modulating Autophagy to Treat Cardiovascular Disease, is one of the 57 funded thus far by the foundation (http://www.leducq-autophagy.org/). The main goal of our Network is to elucidate the roles of autophagy in CVD and discover therapeutic opportunities that autophagy can offer for these syndromes (Figure 1). To this end, we brought together basic research laboratories (Ana Maria Cuervo, Guido Kroemer, Beth Levine, and Luca Scorrano) investigating fundamental mechanisms of autophagy, metabolism, and cellular quality control mechanisms and investigators (Evripidis Gavathiotis, Richard Kitsis, Kinya Otsu, Junichi Sadoshima, and Judith Sluimer) working on the role of autophagy, metabolism, and cell death in CVD. Like all Leducq Transatlantic Networks of Excellence (TNE), we have 2 coordinators: Sadoshima (North American) and Scorrano (European), although The Rutgers New Jersey Medical School serves as the central coordinating office (Figure 2).

The study of autophagy expanded dramatically since the initial discovery of the core molecular machinery by Nobel Laureate Dr Yoshinori Ohsumi. Autophagy evolved to acquire far more diverse functions than the original response to nutrient paucity. Autophagy, a process in which almost every cellular compartment, including organelles, is transported to lysosomes for recycling, is essential for intracellular quantity and quality control. In all mammalian cells, 3 main types of autophagy coexist: macroautophagy, chaperone-mediated autophagy (CMA), and microautophagy. Nonetheless, almost all work in the cardiovascular system to date has focused on macroautophagy, in which double-membrane vesicles, called autophagosomes, transport molecules and organelles to lysosomes to be degraded and recycled. Many groups within this TNE have substantially contributed to building the core of knowledge about the molecular mechanisms of autophagy and CVD. One of the central molecular players in macroautophagy, Beclin 1, was identified by Levine's group.[1] Scorrano, Levine, Kroemer, Kitsis, Sadoshima, and Otsu have made breakthrough contributions to the understanding of the autophagic culling of defective mitochondria (called mitophagy) and its inter-relationships with cell death.[2–4] Sadoshima and Otsu have also described the role of macroautophagy in the physiology of the heart and during heart failure.[5] Macroautophagy is also an important regulator in the vasculature, preventing progression of atherosclerosis via efferocytosis, as shown by Sluimer.[6] CMA, another highly selective type of autophagy in which chaperones bind to recognition motifs in specific proteins and transport them to lysosomes for recycling, was discovered by Cuervo. Little is known yet about the role of CMA in CVD, but it has been shown to play an essential regulatory role in glucose and lipid metabolism.[7] Macroautophagy and CMA are differentially modulated by various stresses in a highly context-dependent manner, and any failure in this tight regulation can contribute to the pathogenesis of a wide variety of CVDs. However, there is still a wide gap of knowledge that must be filled to truly understand the reciprocal interplay between autophagy and CVD. Our TNE hypothesized that (1) autosis, a novel form of cell death by autophagy discovered by Levine's group,[8] is important in the pathogenesis of ischemic injury, heart failure, and atherosclerosis; (2) CMA and cardiovascular metabolism reciprocally modulate each other's functions; (3) mitophagy and mitochondria reciprocally modulate each other's functions; and (4) specific modulators of macroautophagy, CMA, and autosis can provide novel therapies for CVD. To address these hypotheses, our TNE wishes to (1) determine the contribution of autosis, as well as other forms of autophagy-related cell death, to the pathogenesis of CVD; (2) delineate the roles of macroautophagy and CMA as mediators of the metabolic derangements in CVD and the reciprocal dysregulation of autophagy by alterations in cardiovascular metabolism; (3) identify novel molecular mechanisms mediating mitophagy and the contribution of mitophagy to the pathogenesis of CVD; and (4) determine whether pharmacological manipulation of macroautophagy, CMA, and autosis can provide novel therapeutic approaches to CVD. Each of these scientific topics is being studied by several Network

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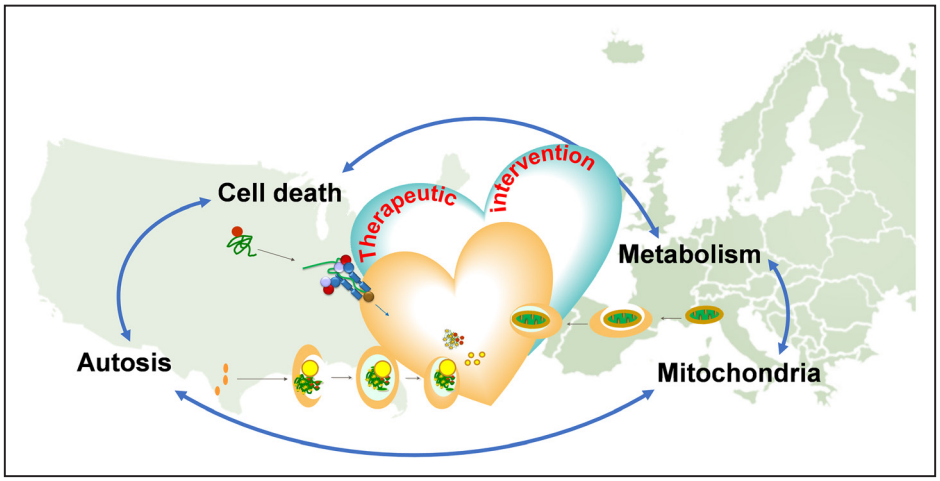

Figure 1. Aims of the Leducq Network Modulating Autophagy to Treat Cardiovascular Disease. The Network has 4 major goals. (1) To evaluate whether autophagy is protective or damaging. (2) To elucidate bidirectional regulation between metabolism and autophagy (particularly in the form of chaperone-mediated autophagy [CMA]). (3) To elucidate bidirectional regulation between mitophagy and mitochondrial metabolism. (4) To discover how therapeutic modulation of autophagy can be used to treat cardiovascular disease (CVD).

laboratories, taking advantage of the expertise, discovery platforms, reagents, and mouse models available in each laboratory. One of the unique features of this Network is the inclusion of several groups with expertise in small molecule design and discovery, such as that of Gavathiotis. Cuervo, in collaboration with Gavathiotis, described the first generation of small molecules that activate CMA.[9] Also, in collaboration with Gavathiotis, Scorrano is screening for small molecules that modulate mitochondrial dynamics and mitophagy. To apply these small molecules, Scorrano is studying the role of novel mediators in myocardial injury and heart failure. Along those lines, Scorrano's group has shown how changes in mitochondrial morphology affect the function of the heart, using OPA1 (dynamin-like 120 kDa protein)-deficient mice as a model.[10] Sadoshima's laboratory, in collaboration with Levine's laboratory, has shown that mitophagy is downregulated in the heart during pressure overload, whereas rescue of mitophagy by the synthetic peptide TAT (transactivator)-Beclin 1 alleviates cardiac dysfunction.[11] Kroemer's group is performing extensive drug testing in the field of caloric restriction mimetics and autophagy. Kroemer's laboratory, in collaboration with the Sadoshima and Scorrano laboratories, reported that the natural polyamine spermidine decreases blood pressure, reduces the incidence of CVD, and prolongs lifespan in an autophagy-dependent manner.[12] Very recently, Levine's group has shown that disruption of the regulatory complex formed by beclin 1 and BCL2 (B-cell leukemia/lymphoma 2) promotes extended lifespan and improved healthspan, reducing age cardiac alterations in aging mice with increased autophagy.[13] Aspirin has recently been shown by Kroemer's group, in collaboration with Sadoshima's group, to recapitulate the effects of caloric restriction mimetics.[14] Another caloric restriction mimetics, trehalose, was shown by Sciarretta and Sadoshima to reduce myocardial infarction–induced cardiac remodeling through

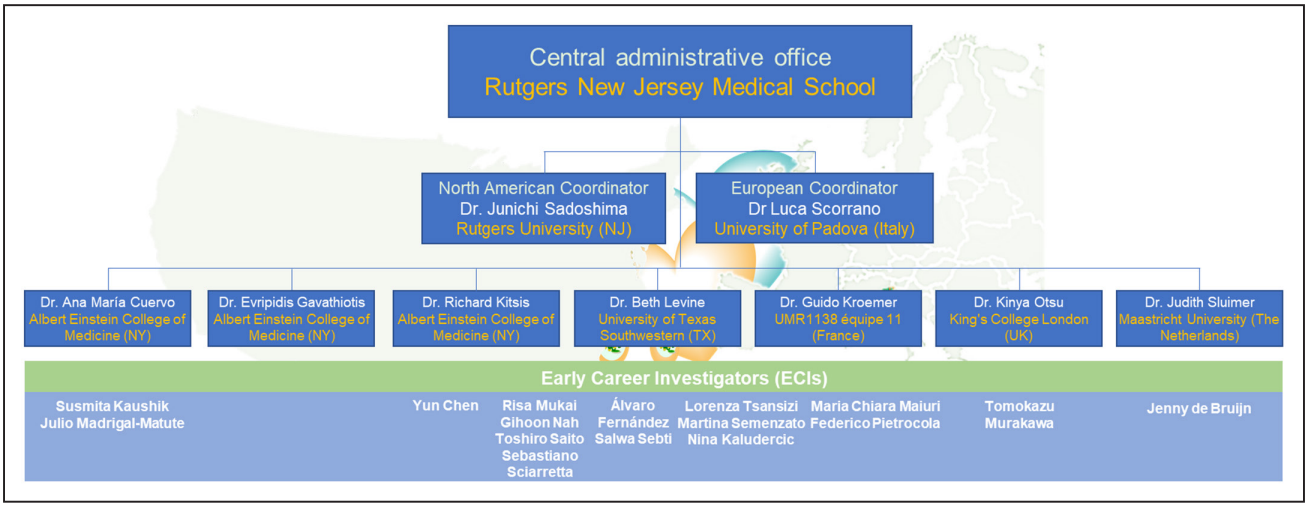

Figure 2. Schematic organization of the Network. The Network unites 8 principal investigators (plus Dr Evripidis Gavathiotis's group) from 4 laboratories each in North America and Europe. Rutgers New Jersey Medical School serves as a central administrative office for fiscal reporting. Each laboratory designated several early career investigators (ECIs). The ECIs form their own Network and actively participate in the activity of the Network. For example, they use the resources of the Network to invite keynote speakers to our face-to-face meetings and visit one another's laboratories to conduct experiments and learn new techniques. In addition, a small number of internal grants are available to support the collaborative projects of ECIs.

induction of autophagy. Trehalose improved both systolic and diastolic left ventricular function associated to a reduction in cardiac hypertrophy, apoptosis, and fibrosis.[15] Thus, this TNE uses a transversal approach by deciphering the very basic molecular determinants of autophagy and CVD to apply successful therapies in humans.

One of the most important goals of this Network is the grooming of early career investigators (ECIs), a group of 1 or 2 fellows or junior faculty for each Principal Investigator, to ensure the future of the next generation of leaders in the field. (https://static1.squarespace.com/static/561565dce4b080a87f1474fa/t/5acbd639f950b74252441c66/1523308090541/Leducq%2BECIs%2Bbiosketch2.pdf). The activity of the ECI group is monitored by the ECI director, Cuervo.

To foster transatlantic interaction, the Network holds biannual face-to-face meetings alternating on each continent. These meetings stimulated informal contact among all Network members, including ECIs. The ECI committee participates in the organization of our Network, selecting Keynote speakers for the biannual meetings. This committee also prepares the program for a satellite ECI meeting, in which established Principal Investigators address career-oriented talks, grant writing, and manuscript preparation. These meetings provide the ECIs with a setting for first-hand interactions with diverse established scientists and their trainees.

In addition to the face-to-face meetings, the Network holds regular online meetings in which all Network members discuss the diverse issues raised during the development of this grid of collaborations and explore additional collaborative opportunities. Independently, the ECI Network holds additional bimonthly online meetings to advance the goals of the organization and promote the successful career development of its members.

A further benefit for the ECIs was the establishment of Junior Investigator internal grant awards. This has been an opportunity for the students, postdocs, and junior faculty to improve their skills in grant writing by receiving feedback from the Principal Investigators in the hosting laboratories and by external review. Moreover, this award has been helpful in promoting collaborations among the trainees of the Network and will hopefully serve as the first step toward fostering long-lasting collaborations after the ECIs become fully independent.

To facilitate synergy among the distinct groups, and especially to expand the collaborative Network of the ECIs, the TNE has set aside funds to support short- and long-term exchanges of the young scientists within the Network. This has already resulted in multiple exchanges between the continents and is helping the TNE ECIs to acquire from other groups the expertise necessary to successfully develop their own projects.

To date, the outcomes of this TNE have far surpassed our original expectations at the scientific, productivity, and exchange levels. The Leducq TNE in Autophagy and CVD is providing a unique framework for the successful development of synergy between diverse transatlantic groups with the common goal of understanding the molecular mechanisms and the functional significance of autophagy in CVD. Considering the progress of the different projects and the productivity of the multiple ongoing collaborations, we anticipate that the platform provided by this award will be highly effective, providing the basis for new therapeutic avenues for CVD and their implementation in prospective clinical trials.

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Disclosures

None.

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