

## *Curriculum vitae*

*Surname:* **RIZZUTO**

*First name:* **ROSARIO**

*Affiliation and official address:* Dept. Biomedical Sciences, University of Padova, Via Ugo Bassi 58/B, 35121 Padova, Italy

*Date and place of birth:* Rome (Italy), April 15<sup>th</sup>, 1962    *Nationality:* Italian

### **Education and career**

#### *Education and training*

1986: Medical degree (University of Padova, Italy) summa cum laude

1986: National Board (“Abilitazione alla professione di medico-chirurgo”)

1987-88: 2-year research stage at the H. Merritt Center for the Study of Neuromuscular disorders (laboratory of Prof. Eric A. Schon), Columbia University, New York, USA

1991: Ph.D. in Molecular and Cellular Biology and Pathology (University of Padova, Italy)

#### *Career/Employment*

1991-1992: Research Associate (University of Padova)

1992-1998: Assistant Professor of General Pathology, School of Medicine, University of Padova

1998-2002: Associate Professor of General Pathology, School of Pharmacy, University of Ferrara

2002-2008: Professor of General Pathology, School of Pharmacy, University of Ferrara

2008-date: Professor of General Pathology, School of Medicine, University of Padova

#### *Academic and administrative duties*

2002-2004: Member of the Research Council of the University of Ferrara

2004-2008: Member of the Senate of the University of Ferrara

2005-2008: Coordinator of the Genetics and Biotechnology network of the Emilia-Romagna region (ER-GenTech)

2006-2008 Dean of the Pharmacy School of the University of Ferrara

2009-2011 Director of the Department of Experimental Biomedical Sciences of the University of Padova

2012-date: Director of the Department of Biomedical Sciences of the University of Padova

2012-date: Member of the Senate of the University of Padova

### **Research activity**

#### *Research interests and career highlights*

By developing an innovative methodology, organelle targeting of recombinant luminescent (aequorin, luciferase) and fluorescent (GFP) proteins, that allowed novel insight in the fields of calcium signalling, cellular metabolism and organelle morphology (Rizzuto et al., *Nature* 358, 325-328, 1992; *Curr. Biol.* 5, 635-642, 1995; Jouaville et al., *Proc. Natl. Acad. Sci. USA* 96, 13807-13812, 1999). These new concepts include the participation of mitochondria in cellular Ca<sup>2+</sup> homeostasis and their role in translating calcium signals in effects as diverse as stimulation of metabolism and induction of cell death (Rizzuto et al. *Science* 262, 744-747, 1993; Brini et al., *Nat. Med.* 5, 951-954, 1999; Pinton et al. *J. Cell Biol.* 148, 857-862, 2000;

*EMBO J.* 20, 2690-2701, 2001), the occurrence of tight signalling interactions between the ER and mitochondria (Rizzuto et al. *Science* 280, 1763-1766, 1998), the identification of the Golgi apparatus as an agonist-sensitive Ca<sup>2+</sup> store (Pinton et al., *EMBO J.* 18, 5298-5308, 1998), the major Ca<sup>2+</sup> rises occurring under the plasma membrane upon cell stimulation (Marsault et al. *EMBO J.* 16, 1575-1581, 1997), to cite a few. In 2011, Prof. Rizzuto has identified the mitochondrial calcium uniporter (MCU), the only fundamental component of the cellular calcium signalling machinery yet to be discovered (De Stefani et al., *Nature* 476, 338-340, 2011). This result has opened the molecular era of mitochondrial Ca<sup>2+</sup> homeostasis, that combines molecular insight into the structure/function relationship of MCU and its regulators (Raffaello et al., *EMBO J.* 32, 2362-2376; Patron et al. *Mol. Cell* 53, 726-37) and the possibility of manipulating mitochondrial Ca<sup>2+</sup> handling in cultured cells and animal models, to clarify its role in the physiological regulation of tissues and in the pathogenesis of the most prevalent human diseases (neurodegenerative disorders, ischemic heart disease, cancer).

#### *Publications*

Prof. Rizzuto published 228 papers on peer-reviewed journals listed on Pubmed (**ISI Web of Science: total citations >20.000, h-index 74**), 14 book chapters and >200 meeting abstracts

#### *Granted Patents:*

“Method for the detection of intracellular parameters with luminescent protein probes for the screening of molecules capable of altering said parameters” (International publication number WO 2005/093429)

“Chimeric proteins for the measurement of ATP concentrations in the pericellular space and relative screening method” (International publication number WO 2006/126231).

#### *Honours, Awards, Editorial Activity*

Prof. Rizzuto is member of the Academia Europaea and of the European Molecular Biology Organization (EMBO). He was awarded scientific prizes: the Chiara D’Onofrio Prize, the Biotec award, the Theodore Bucher Medal. Prof. Rizzuto routinely acts as reviewer for international scientific journals (*Nature*, *Science*, *J. Cell Biol.*, *EMBO J.*, *J. Biol. Chem.*, *Trends Cell Biol.*, etc.) and granting agencies (European Union, Wellcome Trust, BBSRC, NIH, etc.).

#### *Meeting participation and organization*

Prof. Rizzuto gave >200 lectures at national and international meetings (e.g. Gordon Conferences, FASEB Summer Conferences, Keystone Symposia, FEBS, EBEC, ECDO), including >20 plenary lectures. He organized the 12<sup>th</sup> International Symposium on Calcium Binding Proteins and Calcium Function in Health and Disease (Cavalese February 2002), the EMBO Workshop on “Calcium signaling and diseases” (Capri, September 2004) (organizers: E. Carafoli, R. Rizzuto) and the Gordon Conference on Calcium Signalling (Il Ciocco, June 2013)

#### *Awards and Academic Memberships*

Prof. Rizzuto is member of the Academia Europaea and of the European Molecular Biology Organization (EMBO). He was awarded scientific prizes: the Chiara D’Onofrio Prize, the Biotec award, the Theodore Bucher Medal.

#### *Funding ID*

The research in Prof. Rizzuto’s lab is funded by grants from the European Research Council (Ideas Advanced grant), the NIA (Program Project), The Italian Ministries of Education (FIRB) and Health (Ricerca Finalizzata), the Italian Association for Cancer Research (AIRC) and Telethon-Italy, and the Cariparo and Cariplo bank foundations.

## Publication list

1. Alberio T, Mammucari C, D'Agostino G, Rizzuto R, Fasano M. Altered dopamine homeostasis differentially affects mitochondrial voltage-dependent anion channels turnover. *Biochim Biophys Acta*. 2014
2. O-Uchi J, Jhun BS, Xu S, Hurst S, Raffaello A, Liu X, Yi B, Zhang H, Gross P, Mishra J, Ainsbinder A, Kettlewell S, Smith GL, Dirksen RT, Wang W, Rizzuto R, Sheu SS. Adrenergic signaling regulates mitochondrial  $Ca^{2+}$  uptake through pyk2-dependent tyrosine phosphorylation of the mitochondrial  $Ca^{2+}$  uniporter. *Antioxid Redox Signal*. 2014
3. De Stefani D, Rizzuto R. Molecular control of mitochondrial calcium uptake. *Biochem Biophys Res Commun*. 2014
4. de Bernard M, Rizzuto R. Toll-like receptors hit calcium. *EMBO Rep*. 2014
5. Patron M, Checchetto V, Raffaello A, Teardo E, Vecellio Reane D, Mantoan M, Granatiero V, Szabò I, De Stefani D, Rizzuto R. MICU1 and MICU2 finely tune the mitochondrial  $Ca^{2+}$  uniporter by exerting opposite effects on MCU activity. *Mol Cell*. 2014
6. Rossato M, Granzotto M, Macchi V, Porzionato A, Petrelli L, Calcagno A, Vencato J, De Stefani D, Silvestrin V, Rizzuto R, Bassetto F, De Caro R, Vettor R. Human white adipocytes express the cold receptor TRPM8 which activation induces UCP1 expression, mitochondrial activation and heat production. *Mol Cell Endocrinol*. 2014
7. Dyar KA, Ciciliot S, Wright LE, Biensø RS, Tagliazucchi GM, Patel VR, Forcato M, Paz MI, Gudiksen A, Solagna F, Albiero M, Moretti I, Eckel-Mahan KL, Baldi P, Sassone-Corsi P, Rizzuto R, Bicciato S, Pilegaard H, Blaauw B, Schiaffino S. Muscle insulin sensitivity and glucose metabolism are controlled by the intrinsic muscle clock. *Mol Metab*. 2014
8. Logan CV, Szabadkai G, Sharpe JA, Parry DA, Torelli S, Childs AM, Kriek M, Phadke R, Johnson CA, Roberts NY, Bonthron DT, Pysden KA, Whyte T, Munteanu I, Foley AR, Wheway G, Szymanska K, Natarajan S, Abdelhamed ZA, Morgan JE, Roper H, Santen GW, et al. Loss-of-function mutations in MICU1 cause a brain and muscle disorder linked to primary alterations in mitochondrial calcium signaling. *Nat Genet*. 2014
9. Granatiero V, Patron M, Tosatto A, Merli G, Rizzuto R. Using targeted variants of aequorin to measure  $Ca^{2+}$  levels in intracellular organelles. *Cold Spring Harb Protoc*. 2014
10. Granatiero V, Patron M, Tosatto A, Merli G, Rizzuto R. The use of aequorin and its variants for  $Ca^{2+}$  measurements. *Cold Spring Harb Protoc*. 2014
11. Hohl M, Ardehali H, Azuaje FJ, Breckenridge RA, Doehner W, Eaton P, Ehret GB, Fujita T, Gaetani R, Giacca M, Hasenfuß G, Heymans S, Leite-Moreira AF, Linke WA, Linz D, Lyon A, Mamas MA, Orešič M, Papp Z, Pedrazzini T, Piepoli M, Prosser B, et al. Meeting highlights from the 2013 European Society of Cardiology Heart Failure Association Winter Meeting on Translational Heart Failure Research. *Eur J Heart Fail*. 2014
12. Hill JM, De Stefani D, Jones AW, Ruiz A, Rizzuto R, Szabadkai G. Measuring baseline  $Ca^{2+}$  levels in subcellular compartments using genetically engineered fluorescent indicators. *Methods Enzymol*. 2014

13. Bonora M, Giorgi C, Bononi A, Marchi S, Patergnani S, Rimessi A, Rizzuto R, Pinton P. Subcellular calcium measurements in mammalian cells using jellyfish photoprotein aequorin-based probes. *Nat Protoc.* 2013
14. Raffaello A, De Stefani D, Sabbadin D, Teardo E, Merli G, Picard A, Checchetto V, Moro S, Szabò I, Rizzuto R. The mitochondrial calcium uniporter is a multimer that can include a dominant-negative pore-forming subunit. *EMBO J.* 2013
15. Szabadkai G, Rizzuto R. Καλός και Αγαθός: how mitochondrial beauty translates into biological virtue. *Curr Opin Cell Biol.* 2013
16. Sandri M, Barberi L, Bijlsma AY, Blaauw B, Dyar KA, Milan G, Mammucari C, Meskers CG, Pallafacchina G, Paoli A, Pion D, Roceri M, Romanello V, Serrano AL, Toniolo L, Larsson L, Maier AB, Muñoz-Cánoves P, Musarò A, Pende M, Reggiani C, Rizzuto R, et al. Signalling pathways regulating muscle mass in ageing skeletal muscle: the role of the IGF1-Akt-mTOR-FoxO pathway. *Biogerontology.* 2013
17. Patron M, Raffaello A, Granatiero V, Tosatto A, Merli G, De Stefani D, Wright L, Pallafacchina G, Terrin A, Mammucari C, Rizzuto R. The mitochondrial calcium uniporter (MCU): molecular identity and physiological roles. *J Biol Chem.* 2013
18. Tarasov AI, Semplici F, Li D, Rizzuto R, Ravier MA, Gilon P, Rutter GA. Frequency-dependent mitochondrial Ca(2+) accumulation regulates ATP synthesis in pancreatic  $\hat{I}^2$  cells. *Pflugers Arch.* 2013
19. Marchi S, Lupini L, Patergnani S, Rimessi A, Missiroli S, Bonora M, Bononi A, Corrà F, Giorgi C, De Marchi E, Poletti F, Gafà R, Lanza G, Negrini M, Rizzuto R, Pinton P. Downregulation of the mitochondrial calcium uniporter by cancer-related miR-25. *Curr Biol.* 2013
20. Ghislat G, Patron M, Rizzuto R, Knecht E. Withdrawal of essential amino acids increases autophagy by a pathway involving Ca<sup>2+</sup>/calmodulin-dependent kinase kinase- $\beta$  (CaMKK- $\beta$ ). *J Biol Chem.* 2012
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23. Konstantinidis K, Lederer WJ, Rizzuto R, Kitsis RN. Mitofusin 2 joins the sarcoplasmic reticulum and mitochondria at the hip to sustain cardiac energetics. *Circ Res.* 2012
24. Maltecca F, De Stefani D, Cassina L, Consolato F, Wasilewski M, Scorrano L, Rizzuto R, Casari G. Respiratory dysfunction by AFG3L2 deficiency causes decreased mitochondrial calcium uptake via organellar network fragmentation. *Hum Mol Genet.* 2012
25. Rizzuto R, De Stefani D, Raffaello A, Mammucari C. Mitochondria as sensors and regulators of calcium signalling. *Nat Rev Mol Cell Biol.* 2012
26. Drago I, De Stefani D, Rizzuto R, Pozzan T. Mitochondrial Ca<sup>2+</sup> uptake contributes to buffering cytoplasmic Ca<sup>2+</sup> peaks in cardiomyocytes. *Proc Natl Acad Sci U S A.* 2012
27. Raffaello A, De Stefani D, Rizzuto R. The mitochondrial Ca(2+) uniporter. *Cell Calcium.* 2012
28. Rojas-Rivera D, Armisen R, Colombo A, Martínez G, Eguiguren AL, Díaz A, Kiviluoto S, Rodríguez D, Patron M, Rizzuto R, Bultynck G, Concha ML, Sierralta J, Stutzin A, Hetz C. TMBIM3/GRINA is a novel unfolded protein response (UPR) target gene that

- controls apoptosis through the modulation of ER calcium homeostasis. *Cell Death Differ.* 2012
29. Nowikovsky K, Pozzan T, Rizzuto R, Scorrano L, Bernardi P. Perspectives on: SGP symposium on mitochondrial physiology and medicine: the pathophysiology of LETM1. *J Gen Physiol.* 2012
  30. Anelli T, Bergamelli L, Margittai E, Rimessi A, Fagioli C, Malgaroli A, Pinton P, Ripamonti M, Rizzuto R, Sitia R. Ero1 $\alpha$  regulates Ca(2+) fluxes at the endoplasmic reticulum-mitochondria interface (MAM). *Antioxid Redox Signal.* 2012
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  32. Casarin A, Giorgi G, Pertegato V, Siviero R, Cerqua C, Doimo M, Basso G, Sacconi S, Cassina M, Rizzuto R, Brosel S, Davidson M, Dimauro S, Schon EA, Clementi M, Trevisson E, Salviati L. Copper and bezafibrate cooperate to rescue cytochrome c oxidase deficiency in cells of patients with SCO2 mutations. *Orphanet J Rare Dis.* 2012
  33. Rimessi A, Zecchini E, Siviero R, Giorgi C, Leo S, Rizzuto R, Pinton P. The selective inhibition of nuclear PKC $\zeta$  restores the effectiveness of chemotherapeutic agents in chemoresistant cells. *Cell Cycle.* 2012
  34. De Stefani D, Bononi A, Romagnoli A, Messina A, De Pinto V, Pinton P, Rizzuto R. VDAC1 selectively transfers apoptotic Ca $^{2+}$  signals to mitochondria. *Cell Death Differ.* 2012
  35. Tarasov AI, Semplici F, Ravier MA, Bellomo EA, Pullen TJ, Gilon P, Sekler I, Rizzuto R, Rutter GA. The mitochondrial Ca $^{2+}$  uniporter MCU is essential for glucose-induced ATP increases in pancreatic  $\beta$ -cells. *PLoS One.* 2012
  36. De Stefani D, Raffaello A, Teardo E, Szabò I, Rizzuto R. A forty-kilodalton protein of the inner membrane is the mitochondrial calcium uniporter. *Nature.* 2011
  37. Giorgi C, Romagnoli A, Agnoletto C, Bergamelli L, Sorrentino G, Brini M, Pozzan T, Meldolesi J, Pinton P, Rizzuto R. Translocation of signalling proteins to the plasma membrane revealed by a new bioluminescent procedure. *BMC Cell Biol.* 2011
  38. Mammucari C, Patron M, Granatiero V, Rizzuto R. Molecules and roles of mitochondrial calcium signaling. *Biofactors.* 2011
  39. Raffaello A, Rizzuto R. Mitochondrial longevity pathways. *Biochim Biophys Acta.* 2011
  40. Mbaya E, Oulès B, Caspersen C, Tacine R, Massinet H, Pennuto M, Chrétien D, Munnich A, Rötig A, Rizzuto R, Rutter GA, Paterlini-Bréchet P, Chami M. Calcium signalling-dependent mitochondrial dysfunction and bioenergetics regulation in respiratory chain Complex II deficiency. *Cell Death Differ.* 2010
  41. Giorgi C, Ito K, Lin HK, Santangelo C, Wieckowski MR, Lebedzinska M, Bononi A, Bonora M, Duszynski J, Bernardi R, Rizzuto R, Tacchetti C, Pinton P, Pandolfi PP. PML regulates apoptosis at endoplasmic reticulum by modulating calcium release. *Science.* 2010
  42. Mammucari C, Rizzuto R. Signaling pathways in mitochondrial dysfunction and aging. *Mech Ageing Dev.* 2010
  43. Biasiotto R, Aguiari P, Rizzuto R, Pinton P, D'Agostino DM, Ciminale V. The p13 protein of human T cell leukemia virus type 1 (HTLV-1) modulates mitochondrial membrane potential and calcium uptake. *Biochim Biophys Acta.* 2010

44. Mangolini A, Bogo M, Durante C, Borgatti M, Gambari R, Harris PC, Rizzuto R, Pinton P, Aguiari G, del Senno L. NF-kappaB activation is required for apoptosis in fibrocystin/polyductin-depleted kidney epithelial cells. *Apoptosis*. 2010
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47. Rizzuto R, Marchi S, Bonora M, Aguiari P, Bononi A, De Stefani D, Giorgi C, Leo S, Rimessi A, Siviero R, Zecchini E, Pinton P. Ca(2+) transfer from the ER to mitochondria: when, how and why. *Biochim Biophys Acta*. 2009
48. Giorgi C, De Stefani D, Bononi A, Rizzuto R, Pinton P. Structural and functional link between the mitochondrial network and the endoplasmic reticulum. *Int J Biochem Cell Biol*. 2009
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52. Aguiari G, Varani K, Bogo M, Mangolini A, Vincenzi F, Durante C, Gessi S, Sacchetto V, Catizone L, Harris P, Rizzuto R, Borea PA, Del Senno L. Deficiency of polycystic kidney disease-1 gene (PKD1) expression increases A(3) adenosine receptors in human renal cells: implications for cAMP-dependent signalling and proliferation of PKD1-mutated cystic cells. *Biochim Biophys Acta*. 2009
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