Mol Neurobiol (2013) 47:443–445
DOI 10.1007/s12035-013-8407-9

ORBITUARY

On Rita Levi-Montalcini

Gerry Melino · Brian Benedetti · Nicolas Bazan

Published online: 7 February 2013

Rita Levi-Montalcini. 1909–2012.

On December 30, 2012, Rita Levi-Montalcini passed away in her home in Rome at the age of 103 years. Rita was both an inspiration and a model of determination for the young generation not only for her scientific and political achievements, but even more so for her personality, lifelong example, and enthusiasm. Although physically, she was but a tiny frail lady, she showed remarkable determination, perseverance, and endurance both in her character and personality! In fact, Rita was a most popular lady in her own country and well known worldwide.

G. Melino · B. Benedetti
University of Rome Tor Vergata, Rome, Italy

G. Melino (✉)
MRC Toxicology Unit, Leicester, UK
e-mail: melino@uniroma2.it

N. Bazan (✉)
LSU Health Sciences Center, Neuroscience Center of Excellence, New Orleans, LA, USA
e-mail: nbazan@LSUHSC.EDU

Her parents instilled in all their children appreciation for the arts, culture, and intellectual pursuits in a classic Italian style. Her father, Adamo Levi, was a talented engineer, and her mother, Adele Montalcini, a gifted painter. Rita, with her twin sister Paola, was born in Turin on April 22, 1909, the youngest of four children. Gino, the oldest brother, was a professor in architecture at the University of Turin. Anna, 5 years older, was dedicated to literature and humanistic studies. Paola was a gifted painter. Having completed high school, Rita could no longer adjust to the feminine role envisaged by her father and embarked on a career in medical research (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1986/levi-montalcini.html) [1, 2].

The young Rita studied at the University of Turin with a crucial internship under the supervision of the professor of histology, Giuseppe Levi. Remarkably, Giuseppe Levi trained Rita as well as Salvador Luria and Renato Dulbecco, three Nobel laureates, demonstrating the pivotal role of early training. Indeed, all three were colleagues and close friends. It's evident how these early years were critical for her intellectual maturity.

In 1936, Rita graduated in Medicine and Surgery, and began a specialization in neurology and psychiatry. In so doing, she was inspired by the early scientific work of Viktor Hamburger on the effects of wing bud extirpation on the development of the central nervous system in chick embryos [3], pioneered by Drs Lillie and Shorey, who demonstrated the role of unilateral bud extirpation on the developing nervous system. She worked briefly in Brussels before returning to work in Turin with Giuseppe Levi, in the field now known as apoptosis. In 1942, she published a paper in the French journal *Extrait des Archives de Biologie* [4] that dealt with early ideas on the consequences of neurodegeneration in the developing chicken embryo, a process now recognized as occurring via programmed cell death [5–9]. Here, she described the phenomena of *atrophie très*

pronocée, caractérisée par la conglutination des neurofibrilles dans une masse homogène et par l'atrophie du noyau [4]. But in 1943, she was forced to flee a heavily bombed Turin and head to Florence. Here, she worked as a medical doctor, helping war prisoners as well as a population affected by malnutrition and diseases. This was an extremely difficult time for a young Jewish lady in prewar fascist Italy as well as during a long and difficult war.

In 1947, Rita joined the laboratory of Viktor Hamburger in St. Louis, MO. In 1956, Rita was promoted to Associate Professor and 2 years later to Full Professor, a position that she maintained until her retirement in 1977. At that time, she improved the early protocols of Murphy and Karnofsky on the growth of mammalian tumors on the chorioallantoic membrane and transplanted mouse sarcoma tumor 180 to investigate the response of the nerve centers [10]. During these years, she collaborated with Stanley Cohen, when in the early 1950s, she found that mouse tumor cells release a factor that causes rapid growth of nerve cells both in vitro and in vivo [10–13]. This was the work that led to the discovery of the nerve growth factor (NGF), and Rita and Stanley Cohen shared the Nobel prize in Physiology or Medicine for their discovery in 1986 (http://www.nobelprize.org/nobel_prizes/medicine/laureates/1986/levi-montalcini.html) [1]. NGF was identified as a neuronal survival factor well before many other endogenous cell survival ligands. In fact, this discovery was the prototype for the understanding of fundamental mechanisms not only in other members of the neurotrophin family, which include brain-derived neurotrophic factor, neurotrophin-3, and neurotrophin 4/5, but in biology in general. In recent years, NGF has opened novel therapeutic applications and is produced as recombinant human protein (rhNGF) [14]. As an example, glaucoma patients treated with NGF demonstrate long-lasting improvements in the visual field, optic nerve function, contrast sensitivity, and visual acuity by reducing retinal ganglion cell loss [15].

In 1962, Rita established a neurobiology laboratory in Rome, working both in Rome and St. Louis. At the Institute of Cell Biology, part of the Italian National Council of Research, Rita worked with Piero Calissano, Luigi Aloe, and Antonino Cattaneo. To further develop basic and applied research on NGF, as well as on neurodegenerative diseases, and to attract world-class neuroscientists to Rome, she set up the European Brain Research Institute (EBRI), also in Rome, in 2002. The work at EBRI, currently led by Pino Nisticó and where one of us (GM) had the honor to be scientific director, covers a wide range of neurodegenerative pathologies, as reflected in the content of the reviews published on the occasion of her 102nd birthday [16–24]. She was active until her very last moment, expanding fundamental mechanisms of the neurons to the chromaffin cells [25] or, returning to her initial interest, investigating axial rotation during the early stages of chick embryo development [26]. Indeed, both NGF and its receptors TrkA and p75(NTR) are expressed at the very early stages of avian embryo development, well before its effect on sympathetic and sensory neurons; here, NGF regulates somite survival and axial rotation, a crucial developmental process linked to left–right asymmetry specification [26]. Rita was a member of the Accademia dei Lincei, the Pontifical Academy of Science, the National Academy of Sciences in the USA, and the Royal Society.

In addition to her medical interests, Rita dedicated growing attention to social themes on ethics and women. In 1943–1944, she was in close contact with friends and courageous partisans of the "Partito di Azione." She then worked as a medical doctor and was assigned to a camp of war refugees, where epidemics and infectious diseases were undermining the life of the suffering, weak, undernourished victims of war with a daily danger of death. In more recent years, the "Rita Levi Montalcini Foundation" has supported education for thousands of African women. Rita has published more than 20 books disseminating ideas that are a model for the younger generation. In 2001, she was nominated Senator for life by the President of Italy, Carlo Azeglio Ciampi, and she was a strong supporter of the Romano Prodi government. Rita, with her immaculate popularity, was often invited to speak at social events (http://www.youtube.com/watch?v=60VCfca_xE0, http://www.youtube.com/watch?v=BdVCxZOteFY, http://www.youtube.com/watch?v=HkXGTjBS4N8).

In the words of Rita, "*If I die tomorrow or in a year, it is the same—it is the message you leave behind you that counts, and the young scientists who carry on your work.*" She will live on in all our hearts.

References

1. Odelberg W (ed) (1987) Les Prix Nobel. The Nobel prizes 1986. Nobel Foundation, Stockholm
2. Abbott A (2009) One hundred years of Rita. Nature 458:564–567
3. Hamburger VJ (1934) The effects of wing bud extirpation on the development of the central nervous system in chick embryos. Exper Zool 68:449–494
4. Levi-Montalcini R, Levi G (1942) Les consequences de la destruction d'un territoire d'innervation peripheique sur le developments des centres nerveux correspondents dans l'embryon de poulet. Extrait Arch Biol LIII:536–545
5. Melino G (2001) The sirens' song. Nature 412:6842–23
6. Galluzzi L, Vitale I, Abrams JM, Alnemri ES, Baehrecke EH, Blagosklonny MV, Dawson TM, Dawson VL, El-Deiry WS, Fulda S, Gottlieb E, Green DR, Hengartner MO, Kepp O, Knight RA, Kumar S, Lipton SA, Lu X, Madeo F, Malorni W, Mehlen P,

Nuñez G, Peter ME, Piacentini M, Rubinsztein DC, Shi Y, Simon HU, Vandenabeele P, White E, Yuan J, Zhivotovsky B, Melino G, Kroemer G (2012) Molecular definitions of cell death subroutines: recommendations of the nomenclature committee on cell death 2012. Cell Death Differ 19(1):107–120
7. Vandenabeele P, Melino G (2012) The flick of a switch: which death program to choose? Cell Death Differ 19(7):1093–1095
8. Melino G (2011) p63 is a suppressor of tumorigenesis and metastasis interacting with mutant p53. Cell Death Differ 18(9):1487–1499
9. Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, Blagosklonny MV, El-Deiry WS, Golstein P, Green DR, Hengartner M, Knight RA, Kumar S, Lipton SA, Malorni W, Nuñez G, Peter ME, Tschopp J, Yuan J, Piacentini M, Zhivotovsky B, Melino G (2009) Classification of cell death: recommendations of the nomenclature committee on cell death 2009. Cell Death Differ 16(1):3–11
10. Cohen S, Levi-Montalcini R, Hamburger V (1954) A nerve growth-stimulating factor isolated from sarcoma as 37 and 180. Proc Natl Acad Sci USA 40(10):1014–1018
11. Cohen S, Levi-Montalcini R (1956) A nerve growth-stimulating factor isolated from snake venom. Proc Natl Acad Sci USA 42(9):571–574
12. Levi-Montalcini R, Cohen S (1956) In vitro and in vivo effects of a nerve growth-stimulating agent isolated from snake venom. Proc Natl Acad Sci USA 42(9):695–699
13. Cohen S, Levi-Montalcini R (1957) Purification and properties of a nerve growth-promoting factor isolated from mouse sarcoma 180. Cancer Res 17(1):15–20
14. Colangelo AM, Finotti N, Ceriani M, Alberghina L, Martegani E, Aloe L, Lenzi L, Levi-Montalcini R (2005) Recombinant human nerve growth factor with a marked activity in vitro and in vivo. Proc Natl Acad Sci USA 102:18658–18663
15. Lambiase A, Aloe L, Centofanti M, Parisi V, Mantelli F, Colafrancesco V, Manni GL, Bucci MG, Bonini S, Levi-Montalcini R (2009) Experimental and clinical evidence of neuroprotection by nerve growth factor eye drops: implications for glaucoma. Proc Natl Acad Sci USA 106(32):13469–13474
16. Levi-Montalcini R, Knight RA, Nicotera P, Nisticó G, Bazan N, Melino G (2011) Rita's 102. Mol Neurobiol 43(2):77–79
17. Killick R, Niklison-Chirou M, Tomasini R, Bano D, Rufini A, Grespi F, Velletri T, Tucci P, Sayan BS, Conforti F, Gallagher E, Nicotera P, Mak TW, Melino G, Knight RA (2011) Agostini M.mmp73: a multifunctional protein in neurobiology. Mol Neurobiol 43(2):139–146
18. Bano D, Agostini M, Melino G, Nicotera P (2011) Ageing, neuronal connectivity and brain disorders: an unsolved ripple effect. Mol Neurobiol 43(2):124–130
19. Cherubini E, Griguoli M, Safiulina V, Lagostena L (2011) The depolarizing action of GABA controls early network activity in the developing hippocampus. Mol Neurobiol 43(2):97–106
20. Salomoni P, Betts-Henderson J (2011) The role of PML in the nervous system. Mol Neurobiol 43(2):114–123
21. de Castro IP, Martins LM, Loh SH (2011) Mitochondrial quality control and Parkinson's disease: a pathway unfolds. Mol Neurobiol 43(2):80–86
22. Simeone A, Di Salvio M, Di Giovannantonio LG, Acampora D, Omodei D, Tomasetti C (2011) The role of Otx2 in adult mesencephalic-diencephalic dopaminergic neurons. Mol Neurobiol 43(2):107–113
23. Rodríguez JJ, Verkhratsky A (2011) Neuroglial roots of neurodegenerative diseases? Mol Neurobiol 43(2):87–96
24. Stark D, Bazan N (2011) Neuroprotectin D1 induces neuronal survival and downregulation of amyloidogenic processing in Alzheimer's disease cellular models. Mol Neurobiol 43(2):131–138
25. Bornstein SR, Ehrhart-Bornstein M, Androutsellis-Theotokis A, Eisenhofer G, Vukicevic V, Licinio J, Wong ML, Calissano P, Nisticò G, Preziosi P, Levi-Montalcini R (2012) Chromaffin cells: the peripheral brain. Mol Psychiatry 17(4):354–358
26. Manca A, Capsoni S, Di Luzio A, Vignone D, Malerba F, Paoletti F, Brandi R, Arisi I, Cattaneo A, Levi-Montalcini R (2012) Nerve growth factor regulates axial rotation during early stages of chick embryo development. Proc Natl Acad Sci USA 109(6), 2009–14