MILESTONE

Neurology's growth factor: 100 years of Rita Levi-Montalcini

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On Wednesday 22 April 2009, Rita Levi-Montalcini, Nobel Prize laureate and discoverer of the first neural growth factor, turned 100 years old. Her scientific work drastically changed basic neuroscience and could have important implications for the treatment of neurological disorders.

Nearly 60 years have passed since Rita Levi-Montalcini discovered the first neurotrophic protein, nerve growth factor (NGF).[1] She described this pivotal finding, made in a laboratory in St Louis, MO, as a "typical fruit of a reductionistic success".[2] Levi-Montalcini had started her career in medicine in Turin, Italy, under the auspices of the neuroanatomist Giuseppe Levi. As part of her research internship there, she investigated the relationship between the developing nervous system and its targets in the periphery and acquired a keen interest and an exceptional skill in neuroanatomy and histological techniques.

Greatly stimulated by a 1934 article[3] by the renowned German neuroembryologist Viktor Hamburger (1900–2001), Levi-Montalcini set out to prove that neurons in the spinal cord depend on feedback from their targets for survival. After publication of her pilot experiments, conducted during the war in a self-made, clandestine laboratory in the basement of her home, she was invited by Hamburger to continue her work in his laboratory at Washington University in St. Louis. Here, his analytical prowess combined with her highly intuitive mind enabled a series of crucial experiments that led to the identification of NGF in 1951. This discovery would change the playing field of neuroscience and would eventually bring Levi-Montalcini the Nobel Prize for Physiology or Medicine in December 1986.

Since the 1950s, Levi-Montalcini has continued to devote her life to the further study and characterization of NGF in the developing CNS and she remains scientifically active to this day. On 22 April 2009, Levi-Montalcini was congratulated by several distinguished scientists, including fellow Nobel laureates Stanley Cohen (who shared the Nobel Prize with Levi-Montalcini), Aaron Ciechanover and Torsten Wiesel, during a special birthday symposium at the Palazzo Senatorio in Rome to celebrate her life and work (Figure 1). These scientists joined Levi-Montalcini in presenting their views on the impact of the discovery of NGF and the role that this and other, subsequently discovered, growth factors, have had and will continue to have in the fields of clinical neurology and basic neuroscience.

Figure 1 | Rita Levi-Montalcini with Stanley Cohen at Levi-Montalcini's birthday symposium "The Brain in Health and Disease" (Pallazo Senatorio, Rome, 22 April 2009). Permission obtained from E. Granitto and the EBRI Foundation, Rome, Italy.

Since the discovery of NGF in the early 1950s, extensive research has revealed that neurotrophins (NGF, brain-derived neurotrophic factor [BDNF], neurotrophin [NT]-3, and NT-4/5) and their receptors (tropomyosin-related kinase [Trk]A, TrkB, TrkC and the low-affinity receptor $p75^{NTR}$) regulate development and preservation of the vertebrate CNS.[4] In the cortical gray matter and hippocampus of the mature CNS, growth factors influence neuronal survival, as well as synaptic function and plasticity.[4] Certain neurotrophins (for example, NGF and BDNF) have been implicated in several neurological conditions, such as Alzheimer disease (AD), inflammatory pain, traumatic brain injury, depression and anxiety, and multiple sclerosis (MS).[5] In light of these findings, therapeutic strategies aimed at modulating growth factors or their receptors are currently being explored. In AD, early memory loss coincides with dysfunction of the cholinergic system, and treatment with cholinesterase inhibitors can improve cognitive function in a subset of patients with the disease.[5] New AD treatments are being developed on the basis of the discovery that the majority of cholinergic cells express receptors for growth factors, and that NGF can increase cholinergic function and reduce spatial memory deficits in rats.[6] PET images have illustrated that surgical implants of transfected fibroblasts expressing NGF in patients with AD slow cognitive decline and increase cortical glucose utilization.[7] The role of BDNF in AD has been less extensively characterized, but stress, for example, was shown to induce reductions in BDNF messenger RNA levels in the hippocampus.[5] Furthermore,

BDNF serum concentrations are reduced in patients with depression, and antidepressants and electroconvulsive therapy lead to increased BDNF serum concentrations and improve the clinical status of these individuals.[5]

In MS, neurotrophic factors released by inflammatory cells might exert neuroprotective effects (so-called autoimmune neuroprotection),[8] and cognitive decline—especially memory impairment—could specifically be targeted by stimulation of the cholinergic system with growth factor mimetics. In the near future, clinically oriented neuroscientific research could be directed at employing neurotrophins or neurotrophin receptor agonists to modulate and stimulate plasticity after focal damage to the brain. For example, studies could focus on identifying the role of neurotrophins in disease-induced functional cortical reorganization, which might allow patients with MS to remain clinically stable for an extended period of time.[9]

Since the early 1950s, Rita Levi-Montalcini has worked tirelessly to continue to unravel the cellular mechanisms involved with NGF signaling. On 11 July, 1959, she and Stanley Cohen procured definitive proof of the tissue specificity of NGF: young mice and rats injected with an NGF-inhibitor showed a near-total shrinkage of ganglion cells along their spine, while other organs remained unaffected.[10] On gazing through the microscope at these neurons, Victor Hamburger predicted that this date would mark a memorable event in neuroscience. His prediction came true; the discovery of NGF became a milestone in neuroscience that enabled the pioneering of research to explore highly disabling neurodegenerative, neuroinflammatory and neuropsychiatric diseases.

I don't suppose I will ever forget Rita's closing speech at the recent Rome symposium. With characteristic, eloquent enthusiasm, she looked back on 80 years of research, and with a clenched fist she stressed the importance of facilitating research for the younger generation as well as education for the less fortunate. She congratulated the presenters of the day, and stood in anxious anticipation of the results from ongoing and planned studies regarding the clinical applicability of neurotrophins. "More people live to be 100 years old," she concluded with a content smile, "but rarely are they so happy".

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Competing interests
The author declares no competing interests.

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EPILEPSY

Is localization-related epilepsy a progressive disorder? Maybe…

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The issue of whether progressive brain injury occurs in pharmacoresistant epilepsy remains important and controversial. A combined longitudinal and cross-sectional MRI study, in which an automated method was used to measure cortical thickness, has demonstrated accelerated brain atrophy in patients with chronic epilepsy.

Is localization-related epilepsy a progressive disorder? In an attempt to address this longstanding question, Bernhardt and colleagues measured cortical thickness and used a surface-based co-registration MRI technique to assess cortical atrophy within and between groups of patients with pharmacoresistant temporal lobe epilepsy (TLE) and normal controls.[1] The researchers found evidence of atrophy in both large cross-sectional and smaller longitudinal samples of patients with TLE. The changes were found not only in the mesial regions, as would be expected in patients with this condition, but also in the frontal and parietal cortices. The application of cortical thickness analysis offers marked advantages compared with other methods that are used for studying disease-related structural brain changes, such as voxel-based morphometry (VBM).[2] Cortical thickness as a concept of brain structure has a higher external validity and can be more directly related to actual neuronal pathology than can gray matter density (as measured by VBM).[3] Intersubject averaging with surface-based approaches,[4] as employed by Bernhardt *et al.*, uses sulcal and gyral patterns to align equivalent cortical structures across different brains. This method directly compares anatomical structures and can more reliably detect subtle cortical changes than can volume-based averaging in a three-dimensional coordinate system.