

Editoriale

NGF: from chick embryo to human's psyche

Centenarian homage to Rita Levi-Montalcini

1942-2009: FROM TURIN TO STOCKHOLM VIA ST. LOUIS AND ROME

The prelude of the nerve growth factor (NGF) saga (1-3) came to light in 1942 when Rita Levi-Montalcini together her mentor, the eminent neuroanatomist Giuseppe Levi, in Turin observed that removal of the limb bud in the chick embryo resulted in reduced numbers of sensory and motor neurons in the spinal ganglia, and thus confirmed Viktor Hamburger's hypothesis that the target-derived signals act to maintain the growth and survival of these neurons. In 1951 in St. Louis, MO, Levi-Montalcini studied the effect of transplantation of a fragment of mouse sarcoma 180 into the body of three-day old chick embryo. Under the microscope, she saw that the tumor tissue induced sympathetic and sensory hyperinnervation of internal organs, and hypothesized that the transplanted tissues released a diffusible agent that stimulated the growth and differentiation of developing nerve cells, hence firstly dubbed this agent "nerve growth-stimulating factor", later named it NGF. In 1956, in attempt to purify the tumor-derived NGF, Levi-Montalcini in collaboration with Stanley Cohen used snake venom as a rich source of phosphodiesterase, a nucleic acid-destroying enzyme, for the separation of nucleic acids and protein fractions in the tumor tissue. To their great surprise, the tumor homogenate containing the snake venom was several thousand-fold more potent in promoting nerve growth than control tumor samples. Later, it was examined the mammalian homologue of the snake venom gland, the submandibular gland, and discovered that the male mouse submandibular glands were even richer source of the same NGF found in both the tumor and the snake venom. Indeed, it was such an unpredictable cascade from mouse sarcoma via snake venom to mouse salivary glands, which born out NGF.

Altogether, the discovery of NGF has been passed a non-Euclidean pathway in cell biology being marked by a rare combination of scientific reasoning, intuition, and chance, the latter "favors only mind that is prepared", quoting Louis Pasteur. Though 35 year have been passed since its original description, the NGF's saga was awarded Nobel prize for medicine or physiology in 1986 (4).

As often occurs, the framework of an initial conception of the physiological significance of newly discovered molecule extents in the light of emerging findings. Clearly, NGF is one of the most exciting examples of this intellectual growth process. Conceived originally as no more than a growth and survival factor for certain neuronal cells, within the last 50 years, Levi-Montalcini herself and her students and disciples mostly in Italy, also dispersed all over the world, have been passing the torch of NGF research from generation to generation. First, NGF family was created and the name "neurotrophin" was given, hence it is now consisting of brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), NT-4/5, NT-6, and NT-7. Second, in addition to their neurotrophic potentials, the neurotrophins, particularly NGF and BDNF, also exert important and often critical immunotrophic, epitheliotropic, metabotropic, and inflammation-, allergy- and tissue repair-associated activities (3,5,6). Paraphrasing Emily Dickinson's poem *The brain is wide than the sky*, when Rita Levi-Montalcini discovered NGF more than 55 years ago, could she possibly have imagined that *The NGF is wider than the neuron*? Indeed, it is extremely rare one scientist to so much valuably contribute to the development of a research field and a scientific paradigm, as she has been doing!

The observation that NGF exerted a crucial stimulatory action on peripheral nerves that lead to the demonstration of its potential clinical application in peripheral neurodegeneration and later to a wide-range of biological activities that contribute to the development of novel therapy to tissue injury. Thus, NGF has been shown to accelerate the rate of wound healing both in normal mice and healing-impaired diabetic mice, and has a potent pharmacological effect in the treatment for ulcer of the skin and cornea in humans.

Moreover, NGF is essential for the health and well being of the nervous system and it is considered a promising candidate for treating brain disorders. It is one the most potent growth factor for brain cholinergic neurons, since influences the proliferation, differentiation, survival and death of many neuronal cells. For example, dysregulation in NGF brain levels have been implicated in neurodegenerative disorders, such as Alzheimer's disease, Huntington's disease, as well as

psychiatric disorders, including depression induced by substance abuse. A role of NGF in psychiatric disorders was first hypothesized after the observations of altered NGF presence of circulating NGF levels in animal model of social isolation and in human parachute jumping (7-9) and the evidence that patients affected by psychiatric disorders were characterized by elevated plasma NGF levels (10-12). This hypothesis is supported by more recent studies that the action of antipsychotic drugs on classical neurotransmitters, such as dopamine, glutamate, and serotonin and on molecules involved in neuronal plasticity and neuroprotection might be due to different effect of these drugs on neurotrophin distribution in the brain. Other emerging findings indicate that obesity-related deficits, such as diabetes and cardiovascular disorders are characterized by significant alterations in NGF synthesis and release (13,14).

Last not least, the actions of neurotrophins are complex and diverse, and they need to design many new studies to determine how these molecules can, under different conditions, both promote and suppress various processes such inflammation, immunity, allergy, food uptake, glucose and lipid metabolism, memory and learning, also neoplasia, wound healing, and hair growth. Overall, this cultivated much a new thinking about the pathogenesis and therapy of various disorders, including neuropsychiatric, allergic and cardiometabolic diseases.

It is our hope that the data and hypotheses presented and discussed in this special issue will foster a tight interaction between basic scientists and clinicians. The issue was born out of the cordial appreciation of the contribution of the Nobel Laureate Professor Rita Levi-Montalcini in her approaching 100-th birthday. Noteworthy, Rome, *Città eterna*, was founded by the twins brother Romolo and Remo on 21 April 753 BC, whereas Rita Levi-Montalcini was born on 22 April 1909 in Turin, Italy.

Cent'annos, Professor Rita Levi-Montalcini!

Luigi, Angela, George

REFERENCES

1. Levi-Montalcini R: The saga of the nerve growth factor. *Neuroreport*, 1998, 9, R71-83.
2. Levi-Montalcini R: From Turin to Stockholm via St. Louis and Rio de Janeiro. *Science*, 2000, 287, 809.
3. Levi-Montalcini R: The Saga of the Nerve Growth Factor. Preliminary Studies, Discovery, Further Development. World Scientific, Singapore, 1997.
4. Levi-Montalcini R: The nerve growth factors 35 years later. *Science*, 1987, 237, 1154-1162.
5. Aloe L, Chaldakov GN (eds): Nerve growth factor in health and disease. *Biomedical Reviews*, 1999, 10.
6. Aloe L, Calzà L (eds): NGF and related molecules in health and disease. *Progress in Brain Research*, 2004, 146.
7. Maestripieri D, De Simone R, Aloe L, Alleva E: Social status and nerve growth factor serum levels after agonistic encounters in mice. *Physiology & Behavior*, 1990, 47, 161-164.
8. Alleva E, Aloe L: Physiological roles of nerve growth factor in adult rodents: a biobehavioral perspective. *International Journal of Comparative Psychology*, 1989, 2, 147-163.
9. Aloe L, Bracci-Laudiero L, Alleva E, Lambiase A, Micera A, Tirassa P: Emotional stress induced by parachute humping enhances blood nerve growth factor levels and the distribution of nerve growth factor receptors in lymphocytes. *PNAS*, 1994, 91, 10440-10444.
10. Bersani G, Aloe L, Iannitelli A, Maselli P, Alleva E, Angelucci F, Pancheri P: Low nerve growth factor (NGF) plasma levels in schizophrenic patients. *Schizophrenia Research*, 1996, 18, 159-160.
11. Bersani G, Iannitelli A, Fiore M, Angelucci F, Aloe L: Data and hypotheses on the role of nerve growth factor and other neurotrophins in psychiatric disorders. *Medical Hypotheses*, 2000, 55, 199-207.
12. Fiore M, Di Fausto V, Iannitelli A, Aloe L: Clozapine or haloperidol in rats prenatally exposed to methylazoxymethanol, a compound inducing entorhinal-hippocampal deficits, alter brain and blood neurotrophins' concentrations. *Annali dell'Istituto Superiore di Sanità*, 2008, 44, 167-177.
13. Chaldakov GN, Fiore M, Hristova MG, Aloe L: Metabotropic potential of neurotrophins: implication in obesity and related diseases? *Medical Science Monitor*, 2003, 9, HY19-21.
14. Chaldakov GN, Fiore M, Stankulov IS, Manni L, Hristova MG, Antonelli A, et al.: Neurotrophin presence in human coronary atherosclerosis and metabolic syndrome: a role for NGF and BDNF in cardiovascular disease? *Progress in Brain Research*, 2004.