In an elegant manner Viviana Triaca presented in this volume of Adipobiology her Homage to Rita Levi-Montalcini highlighting the significance of nerve growth factor (NGF) in the molecular mechanisms of Alzheimer’s disease (AD) (1, also see Note in the References). This remarkable review generates a completely new direction in understanding some of the new and specific aspect of AD pathology, focusing on the NGF modulation of amyloid precursor protein (APP) processing and metabolism. Dr Triaca provides a paradigm shift from “classical” cholinergic to NGF-centered approach showing that the dysregulation of NGF-TrkA (receptor tyrosine kinase A) and proNGF-p75NTR signalling systems is a good candidate for being primus movens in the pathogenesis of AD (1).

Here we spotlights the possible involvement of primary cilium (PC) and PC-associated NGF signaling in the pathogenesis of AD.

As often occurs in the history of biomedical sciences, the presence or even the existence of a newly discovered cellular structure has been “enjoyed” a traditional neophobia. This was also the case with the PC. Hence within the last 15 years the emerging evidences have been demonstrating that in addition to their well-established roles in sight, smell, and mechanosensation, PC is a signaling hub for many physiologically, developmentally and diseased processes (2-5).

Almost all cells in the human body contain a single, primary cilium (PC). Cilia are plasma membrane-microtubule organelles represented by two major phenotypes: (i) motile, 9 + 2 cilia, numerous per certain populations of cells, and (ii) non-motile, primary, 9 + 0 cilia, single per almost all cell types including the neurons (2-5).

Although PC were observed around 1897 by Zimmerman in the renal epithelial cells (cited in 4), conclusive evidence of their existence required the introduction of the electron microscope for biological studies (6-8). Primary cilia control multiple cellular processes (9-14) such as fluid mechanical forces, calcium channel functioning, protein trafficking, and receptor-mediated signal transduction (15 for PC-p75NTR connection). For the pioneering contributions of Poole and colleagues to cilium as cellular “cybernetic probe” functioning via its association with the Golgi complex, see 16,17, also 18.

The unprecedented interest in PC research came after the discovery that PC dysfunction or aciliogenesis is the culprit for many disorders now collectively termed primary ciliopathies, a selected list presented in Table 1. Intriguingly, various neuropsychiatric deseases including Alzheimer’s disease (19-21) were recently also included in the list. In the same vein, obesity is a disorder associated with ciliopathies, such as Bardet-Biedl syndrome and Alström syndrome (22). And leptin, a prototypic adipocyte-secreted protein (adipokine), was implicated in obesity-associated ciliary dysfunction (23). Since obesity patients are prone to the development of AD, and APP is expressed also in the adipose tissue (24), these data may further implicate PC dysfunction in AD neurodegeneration.
Noteworthy, neurons contain both multiple spines on their dendrites as well as PC emanating from their soma. It was suggested that similar to dendritic spines (DS), another plasma membrane-cytoskeletal organelle (25), PC may function like a postsynaptic structure specialized in responding to “presynaptic” environmental stimuli (26,27). Moreover, the formation and plasticity of DS require (i) brain-derived neurotrophic factor (BDNF), the first cousin of NGF, and (ii) not only actin and associated proteins, but also microtubules (28).

As mentioned above, PC expressing the panneurotrophin receptor p75NTR has been found in AD-associated granule cells of the adult hippocampal dentate gyrus in mice (15, see also 19-21,29). Since amyloid beta has been shown to bind p75NTR and induce apoptotic pathway in neurons (1), PC-p75NTR connection might be implicated in the amyloid beta-driven neurodegeneration of AD (see 1 for IGF1 involvement in APP processing, and 30 for PC-IGF1 link).

As Dr Triaca notably states, a focus shift to “the discovery of blood or cerebrospinal fluid markers for early diagnosis, and early therapeutic intervention with modulators of APP processing” is a sign that the dynamics of AD research is undergoing remarkable plasticity. We expect that the next several years will delivered new insights into the significance of these amazing cellular molecules (NGF, p75NTR, BDNF and IGF1) and organelles (PC and DS) in the pathogenesis of AD.

Why not!

Table 1. Selected disorders shown in >200 reports published in 2013*

| 1. Retinal dystrophy and degeneration | Many types |
| 2. Neonatal and fetal death | A multitude of disorders |
| 3. Bardet-Biedl syndrome(s) | Mesoaxialpolydactyly |
| 4. Polycystic kidney disease and injuries | Autosomal dominant and recessive |
| 5. Motor neurone disco-ordination | Absence of well-formed cilia |
| 6. Pre-invasive and invasive prostate cancer | Multi-organ dysgenesis |
| 7. Joubert syndrome | Brain malformations |
| 8. Meckel-Gruber syndrome | Obesity, insulin resistance |
| 9. Nephronophthisis | Atherosclerosis, obesity, diabetes |
| 10. Lowe syndrome | Disorientation of fibers |
| 11. Biliary atresia | |
| 12. Alström syndrome | |
| 13. Cardiometabolic diseases | |
| 14. Mental retardation | |
| 15. Ventricular septal defects | |
| 16. Jeune, Sensenbrenner, and Mainzer-Saldino chondrodysplasia | |
| 17. Lens fiber differentiation | |
| 18. Cholangiocarcinoma | |
| 19. Renal carcinoma | |
| 20. Meier-Gorlin syndrome | |
| 22. Alzheimer’s disease | |
| | NGF-p75NTR-PC link? |

* Modified from Wheatley (4).
Acknowledgments
We wish to thank Denys Wheatley and Anthony Poole for brain-and-heart friendship (BHF), also related to the research in ciliology. And apologize to colleagues whose work was not discussed or cited owing to space limitations.

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