RITA LEVI MONTALCINI: THREE CRUCIAL STEPS TOWARD STOCKOLM

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DISCOVERY OF VEGF, A KEY REGULATOR OF ANGIOGENESIS

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NOVEL EXPERIMENTAL MODELS TO STUDY NEUROTROPHIN FUNCTION

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THE NEXT 50 YEARS OF NGF

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The identification of the first growth factor, NGF, over 50 years ago changed the field of biology in many unexpected ways. Growth factors now have a prominent role in cancer, stem cells, cell differentiation and maladaptive consequences, such as psychiatric and neurodegenerative disorders. What will transpire in the next 50 years? Here we explore unanswered questions related to neurotrophic factors in the future. If solved, the answers would represent breakthroughs with lasting and widespread impact upon many biological problems.

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INTRACELLULAR PROTEIN DEGRADATION: FROM A VAGUE IDEA THROUGH THE LYSOSOME AND THE UBIQUITIN-PROTEASOME SYSTEM AND ON TO HUMAN DISEASES AND DRUG TARGETING

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Between the 1950s and 1980s, scientists were focusing mostly on how the genetic code was transcribed to RNA and translated to proteins, but how proteins were degraded had remained a neglected research area. With the discovery of the lysosome by Christian de Duve it was assumed that cellular proteins are degraded within this organelle. Yet, several independent lines of experimental evidence strongly suggested that intracellular proteolysis was largely non-lysosomal, but the mechanisms involved have remained obscure. The discovery of the ubiquitin-proteasome system resolved the enigma. We now recognize that degradation of intracellular proteins is involved in regulation of a broad array of cellular processes, such as cell cycle and division, regulation of transcription factors, and assurance of the cellular quality control. Not surprisingly, aberrations in the system have been implicated in the pathogenesis of human disease, such as malignancies and neurodegenerative disorders, which led subsequently to an increasing effort to develop mechanism-based drugs.

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LONG-TERM POTENTIATION IN ANIMAL MODELS OF ALZHEIMER'S DISEASE

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The discovery of long-term potentiation (LTP) of hippocampal synaptic transmission, which represents the principal experimental model for the synaptic changes underlying learning and memory, has stimulated over the past years substantial progress in the understanding of pathogenic mechanisms underlying neurodegenerative disorders, such as Alzheimer's disease (AD). Indeed, several lines of evidence point to synaptic dysfunction not only as a core feature but also a leading cause of AD. Following intensive investigations into LTP in AD models, a variety of compounds have been found to rescue LTP impairment via numerous mechanisms. However, very few of these discoveries have been successfully translated into disease-modifying compounds in humans. This review recapitulates the main molecular mechanisms underlying LTP, the synaptic alterations across the different AD models and the disease-modifying strategies targeting amyloid β-protein (Aβ) successfully tested in experimental AD.

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BIOCHEMICAL AND IMAGING MARKERS FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE: AN OVERVIEW

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The major neuropathological hallmarks of Alzheimer's disease (AD), the most common form of neurodegenerative disorder, are the presence of extracellular amyloid plaques and intracellular neurofibrillary tangles. Currently, most biomarker research in AD is focused on either brain imaging or is fluid-based. In the area of fluid biomarker research, cerebrospinal fluid (CSF) has been demonstrated to be an excellent source for biomarkers. Indeed, given that CSF is in the adjacent vicinity of the brain, biochemical alterations in the cerebral tissue affect its biomarker composition. Valid CSF biochemical markers are accessible for amyloid pathology ($A\beta_{1-42}$), neurofibrillary pathology (hyperphosphorylated protein tau, p-tau), and cortical axonal degeneration/damage (total tau, t-tau). The diagnostic sensitivity and specificity of the established "core" CSF biomarkers in discriminating AD from cognitively healthy individuals and from other varieties of dementing pathologies has been satisfactorily accomplished. Notably, a combination of more than one "core" biochemical marker in the CSF is believed to provide higher diagnostic accuracy of AD. Over the last decade, besides CSF biomarkers, there has been a substantial increase of studies concerning neuroimaging techniques for AD. Many of these methods are already employed in routine clinical practice. Magnetic resonance imaging (MRI) is a tool for clinical assessment of dementia patients and offers an important aid to the clinical diagnosis and subtyping of dementia in earlier stages. The main characterized structural MRI biomarker in AD is represented by cortical diffuse atrophy. Diffusion tensor imaging (DTI), investigating white matter microarchitecture and integrity, has been employed in several AD studies. Furthermore, more advanced protocols have been fruitfully utilized in AD. The introduction of machine learning algorithms has made practicable to manage images from different modalities simultaneously and to classify a single subject into a predefined group. These techniques have been identified as promising tools in neuroimaging data analysis. In the future, machine learning algorithms are expected to be integrated into scanner softwares along with all the pre-processing steps necessary to assist the radiological expert in the semi-automated detection of prodromal AD stages based on pattern recognition strategies.

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HUMAN UMBILICAL CORD BLOOD-DERIVED MONONUCLEAR, HEMATOPOIETIC AND NGF-RESPONSIVE STEM CELLS CONFER NEUROPROTECTION IN ISCHEMIC MODELS

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Human umbilical cord blood (HUCB), which is a valuable source for cell therapy of hematologic diseases, was recently found to harbor a population of cells that confer neuroprotection in animal models of brain injury. To explore the neuroprotective properties of cord blood we investigated HUCB-derived mononuclear cells (MNC), $CD45^+$ hematopoietic cells as well as a unique MNC population of a collagen-adherent cells which in the presence of nerve growth factor (NGF) and interferon-gamma (IFN-γ) differentiate in vitro into a neuronal phenotype (termed HUCBNP). In vitro co-culture of MNC with oxygen-glucose-deprived PC12 cells resulted in about 30% neuroprotection, as assessed by decreased LDH release and inhibition of caspase 3 activity, and yielded a decrease by 95% in the level of free radicals, concomitant with the secretion of antioxidants and growth factors, such as NGF into the culture medium. Using a closed head injury (CHI) brain trauma mouse model, we also compared neuroprotective effects of HUCB-derived MNC and $CD45^+$ cells upon either brain intraventricular (icv) or intravenous (iv) transplantation. The in vivo experiments in which iv implantation of MNC or $CD45^+$ cells in mice with TBI indicated a fast 2 h homing of the cells to the brain lesion followed by a progressive neuroprotective effect maintained up to 3 weeks. In conclusion, our studies are in line with other reports and propose that either HUCB-derived MNC or $CD45^+$ fraction may represent a valuable source of neuroprotective cells such as NGF-responsive progenitors for therapy of ischemic disorders such as stroke, brain trauma and myocardial infarct.

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TAKING PAIN OUT OF NGF: PAINLESS NGF FOR ALZHEIMER'S DISEASE THERAPY

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Recent data from different lines of research point to an imbalance in the homeostasis of the NGF system as an upstream driver for Alzheimer's neurodegenerations. In this framework, the first therapeutic choice would be to use NGF itself as a drug. However, it is a challenge to deliver NGF into the brain, in a safe and efficient manner and a clinical application of NGF requires solving two major problems: effective CNS delivery, since NGF does not readily cross the blood-brain-barrier, and, second, the pronociceptive actions of NGF, that is a potent pain sensitizing agent. Inspired by a genetic mutation in the NGF gene, that is found in patients suffering from a rare genetic congenital form of insensitivity to pain (HSAN V), we have engineered painless NGF, a recombinant form of NGF that is traceable against endogenous NGF, has equal neurotrophic potency to NGF but has a 10 fold lower nociceptive activity with respect to NGF. The painless hNGF P61 R100 traceable NGF molecule represents a candidate drug that has the potential for being developed not only into a disease-modifying non invasive therapy for Alzheimer's Disease, as well as for other therapeutic indications.

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NEED FOR NEW GUIDELINES FOR ALZHEIMER'S DISEASE CLINICAL TRIALS

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MESENCEPHALIC CELL CULTURES FROM CYP2E1 KNOCKOUT MICE: A STUDY ON MPP+ TOXICITY

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The relevance of the P450 2E1 isozyme (CYP2E1) in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced parkinsonism in C57bl mice has been reported previously. Recently, we generated mesencephalic cell cultures from Cyp2e1(–/–) and wild-type 129S1/SvImJ (Cyp2e1(+/+)) embryos. In the present study we demonstrated that Cyp2e1(–/–) primary cultures proved to be a valuable in vitro model of 1-methyl-4-phenylpyridinium ion (MPP+) toxicity and metabolic study. After 24 h of MPP+ exposure, Cyp2e1(–/–) mesencephalic cells were less sensitive to the toxic insult compared with Cyp2e1(+/+) cultures. The MPP+ kinetic study revealed long-term enhanced uptake of the toxin inside the neurons with a total retention that was double that of controls. The dose-response study of the long-term retention of MPP+ revealed that the difference is observed only at a low concentration of the toxin. Our data suggest that in Cyp2e1(–/–) cultures, once MPP+ is inside the cells, it enters preferentially into vesicles where its storage represents a sort of protection with respect to other toxic sites such as mitochondria.

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