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Mechanism of Diseases: Non-Degradable Protein Sequences or Genetic Modifications?

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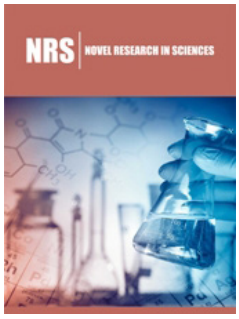

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Abstract

The chemicals modify irreversibly the protein sequences leading to cell death and mitochondrial destruction, altering the protein network. MEMS eliminates the non-degradable protein sequences and restores cell homeostasis eliminating the degenerative process of aging and infection. Genetic modifications lead to wrong protein-protein interactions. MEMS is safe and efficient in mammalians and necessary for better healthcare.

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Introduction

After many years of research experience in biochemistry, microbiology, and molecular biology in Poland and France, I started to work in eye research in 1990 in the Department of Ophthalmology at University Hospital in Zürich. Participating at ARVO congresses, I noticed that there was only a science describing the non-degradable proteins in the eye associated with diseases but any explanation. The researchers knew the small molecules in the eye but did not know how these molecules arose there. Working with bovine and human eyes, I found that the anti-oxidative enzyme Indoleamine-2,3-Dioxygenase (IDO) is present in the eye leading to the formation of the end product xanthurenic acid [1,2].

For 120 years, scientists have known that oxidative stress leads to the development of aging-associated diseases. However, the antioxidants did not stop any illness. The infections lead to acute oxidative stress and induction of the enzyme IDO which binds the singlet oxygen to cleave the tryptophan ring leading to the formation of the kynurenine. The 3-hydroxykynurenine, after transamination, becomes xanthurenic acid. The oxidative tryptophan degradation pathway exists in many organs. I found IDO for the first time in the eye and began work on the pathological role of xanthurenic in hypothesizing that this molecule leads to senile cataract formation [3].

Other researchers considered IDO responsible for the pathology because they observed high IDO activity in the pathological tissue, and such papers they published in leading journals. Very often, partial knowledge leads science to confuse the cause with the effect. Even they built businesses to prepare the IDO inhibitor, which failed. IDO is necessary to prevent oxidative stress and its anti-oxidative enzyme, and its inhibition leads to tissue necrosis. Oxidative stress induces IDO. For this reason, oxidative stress causes high IDO in infection or cancers, leading to high xanthurenic acid. Xanthurenic acid binds covalently and irreversibly to the regulatory protein sequences inducing at first the unfolded response of the stress proteins GRP and further the proteolysis of the non-modified sequences of proteins [4]. Xanturenic acid, after oxidation, became the molecule attaching irreversibly to proteins. In primary human cell culture, xanthurenic acid led to cell death with caspase 3, and PARP activation degraded the DNA, but the cytoskeleton was not degraded but crosslinked [5]. We called this kind of cell death - pathological apoptosis.

The new process explained the cell apoptosis in the disease's development. The high-ranking journals refused to publish the work, and a reviewer at a Keystone Symposium told

me that he declined the paper because if somebody did not issue a report in Nature before, it would not begin to publish in Nature after fifty. The following paper was on mitochondria and showed that xanthurenic acid leads to mitochondrial damage. The process is associated with the degradation of mitochondria with the release of cytochrome C and uncoupling of mitochondrial respiration, resulting in high oxygen consumption and low energy formation and translocating the mitochondrial proteins into the nucleus [6]. The modified proteins change the place, and their role in the cell, e.g., 14-3-3 proteins regulated the Ca2+-calmodulin network bound covalently to calmodulin and impaired the regulation of the calmodulin-binding proteins [7]. Nobody took care of the results. Swiss National Science Foundation (SNSF) interrupted my project's support by explaining that they had money left for project support. Still, they could not support "such a low-quality project." The "high-quality projects" had transgenic mice, which were ill because of gene knockout and even better when they were a double or triple knockout. They were a model for the drug development required by all regulatory agencies. Everybody worked on transgenic mice. The system biology in the wild and transgenic organisms is different. Switzerland, with EU help, prepared a computer center to study the proteins interactions based on the transgenic mice model to resolve the mister of the brain with Parkinson's. SNSF and EU launched projects on the System in Biology and compared the different circuits obtained in transgenic mice. Nature Biotechnology publishes the "scholastic" discussion on systems biology. I wrote to Nature Biotechnology to ask if they understood what they published, but there was no discussion.

In 2011, I published that wild mice have different protein-protein interactions than transgenic mice [8]. These results explained the non-sense of transgenic mice models for the aging-associated degenerative diseases research caused by chemicals.

The wild cells MEF and the cells knockout in Bid and double knockout Bid/Bad growing in the presence of xanthurenic acid had different protein-protein interactions than the wild strain [9]. The paper showed that the use of transgenic mice for drug development did not have any scientific sense. It was taboo for a publication of these results in highly ranked journals, and Nature refused to publish the results sent as "Brief Communication." So, through 20 years, nobody has taken care of the disease's mechanism and problems in the research, and any funding did not support my work. The research and toxicity studies made on the transgenic mice differed from the results in humans in clinical trials leading to the collapse of many businesses. It caused the retraction from these models leading to a new, but still "genetic" trend modifying the DNA matrix with unknown results on the protein-protein interactions, which has an executive role in the cells, a fiasco reported by media almost every day.

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However, the apotheosis for complicated methods, based on the pathology's wrong models, continued providing toxic and non-efficient drugs with debilitating side effects. In health science in the last 30 years, obliged "Programmed Innovation," and even if nobody should program innovation, such an absurd "program" existed in the EU and Switzerland, refusing MEMS that stops cell degeneration by eliminating the non-degradable proteins. They look for "advanced" genetic methods. The EU Commission (FP projects and Innovative Medicine Initiative) and SNSF treated the activity of our innovative molecule against cell degeneration and antibiotic-resistant bacteria with arrogancy and cynicism. They announce the pandemic of antibiotic-resistant strains and a lack of solution. Moreover, to avoid the resistance of antibiotics in animals, they launch programs to produce meat in cell culture-the meat with the wrong protein-protein interactions, then toxic and non-digestible for mammalians - FDA accepts.

All genetic intervention destroys cell homeostasis. CAR-T therapy or DNA modification by CRISPR disrupts homeostasis and modifies the protein-protein interactions leading to pathological consequences. The biased system of publications is associated with partial funding and rejection of all financial support for the research necessary for science in healthcare.

So, to follow the innovation without financial support, we do the work using our family savings. The technology consists of preparing Molecule Establishing Membrane Signaling (MEMS), which are antibodies against the modified regulatory sequences of the proteins, called Intrinsically Disordered Sequences (IDS) (Malina Halina Patent US, CA, JP, EU). IDS are flexible pieces of sequence in the tridimensional structure of the proteins permitted protein-protein interactions and cell homeostasis regulation. The chemicals modify IDS in priority because of their regulatory role, the exposition for the interactions, and their high content of the basic amino acids. The covalent and irreversible modifications of the IDS lead to non-degradable sequences of the proteins accumulated in the protein turnover. The cells do not have any system to degrade the modified protein sequences. The modified IDS polymerize together and are transferred to the cell membranes for elimination by the immune system. So, we prepared the antidote, the chemically modified polymers of regulatory sequences, against the pathology caused by chemicals, which we currently call Molecule Establishing Membranes Signaling (MEMS). Xanthurenic acid modifies in the first line the calmodulin-binding proteins. By outsourcing, we synthesized the peptides and polymerized them by incubation with xanthurenic acid. The rabbit antibodies against the polymer of the peptides remove the modified peptides from the cells and restore the proteins network and the health of the cells. The antibody against the polymer of the peptides stopped cell pathology induced by xanthurenic acid and other chemicals, e.g., cyclophosphamide. The outsourced studies showed that the MEMS heals mice infected with *S. aureus* and restores the immunity suppressed with cyclophosphamide. Cyclophosphamide injected into animals induces immunosuppression, and it is a universal model of immunosuppression.

MEMS heals the wounds of the immunosuppressed -cyclophosphamide mice and establishes the immune cells'

homeostasis, leading to increased CD4 lymphocytes. MEMS rapidly heals the mice. In the primary cell culture in all cells studied, human astrocytes, retinal epithelial cells, and smooth muscle cells MEMS established cell homeostasis, stopping the cells' degeneration, restoring mitochondria and calcium homeostasis, and eliminating the aggregated beta-amyloid. The market has any molecule preventing the elimination of the modified proteins and preventing diseases. So being 58 at this time and without a bench and money to do the clinical research, I started using MEMS carefully on my skin, healing dermatitis, a degenerative and inflammatory skin condition. It was resistant to all treatments for eight years and, like all open wounds, infected with Staphylococcus aureus, which was resistant to all antibiotics.

The small molecules modify the proteins leading to the accumulation of the non-degradable protein sequences and the homeostasis destruction. Only MEMS enables the elimination of them and restores homeostasis in mammalians preventing aging-associated pathology and infections. MEMS is the first molecule to eliminate the modified proteins, the primary cause of cell pathology in aging and infections. The side effects of the chemicals are evident from the current treatments with small molecules in oncology. The therapy is sometimes more difficult for the patients than the disease itself. The covalent and irreversible modifications of proteins, the cause of pathological apoptosis, explain the mechanism of the harmful process. The papers published 20 years ago do not exist for scientists, regulatory authorities, and healthcare officials. Despite that, these publications showed fundamental errors in the current drug discovery approach: the chemicals used as the drugs induce cell degeneration, and the transgenic animal models are inappropriate for the drugs against aging-associated pathology. Pharma company recognized after 20 years that chemically modified proteins cause cell pathologies, making partnerships worth billions to degrade the modified proteins. They prefer to develop ample research to look for a new solution than to adopt MEMS. The degradation of the non-degradable proteins swallowed many billions but led only to high toxicity. They do not have any obligation from the regulatory agencies to correct errors and improve healthcare.

Conflict of Interest

HZ Malina declared a conflict of interest while she developed the research, from 2005 to the present, without sponsoring, and has patented Intrinsically Disordered Sequences technology targeting non-degradable proteins, the cause of pathology.

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