A Niche in Neurodegenerative Disease

Dr Martin Duennwald

Scientia

www.scientiapublications.com

A Niche in Neurodegenerative Disease

Dr Martin Duennwald is an Associate Professor in the Department of Pathology at the Schulich School of Medicine and Dentistry. Here he discusses his latest research project, in which he studied protein misfolding in neurodegenerative diseases.

To start, what inspired you to study protein misfolding and neurodegenerative diseases such as Huntington's disease?

I have always been interested in the mechanisms by which basic biological processes, such as protein misfolding and cellular stress response programs, modulate human diseases. Understanding the underlying basic biological mechanisms motivates my research and keeps me enthralled. Another major reason for my interest in neurodegenerative diseases is the tremendous personal suffering they afflict on patients, their loved ones, and our entire society. At present, there is no real cure for any neurodegenerative disease. I am convinced that by deciphering the basic biological principles underlying these diseases, such as protein misfolding, we will find therapeutic strategies to delay, hold, or even cure these devastating diseases.

The number of patients suffering from neurodegenerative diseases in Canada has reached 700,000 and is expected to double over the next 20 years. Are there any numerical estimates of how much of a burden these diseases place on society in terms of money or human resources such as man hours?

The Alzheimer's Society of Canada estimates that the total cost associated with dementias and other neurodegenerative diseases, combining medical expenses and lost earnings, amounts to a staggering CA $ 33 Billion per year. Notably, the medical expenses alone will exhaust almost the entire Canadian health budget in one generation from now. Certainly, the situation in Canada is not an exception as the World Health Organization deemed neurodegenerative diseases and dementias the most significant health crisis of the 21st century world-wide. Clearly, we have to work on this problem and find solutions soon.

You enlisted a team of experts in each necessary field to conduct your research. What fields were involved and did you involve a number of different institutions? Did coordinating this team present any particular challenges?

In my experience, research is most interesting, most productive, and most fun when conducted in a team of people with different expertise and different ways to think about the same problem. It would be impossible for one researcher to become an expert in the many powerful yet complex experimental techniques of modern biomedical research. However, each of these different approaches adds tremendous value to the study of a particular problem, particularly protein misfolding. In my view, it is only the synthesis of these different approaches that will allow us to answer even the most intricate questions in biology, which will ultimately result in finding effective therapeutic strategies for the treatment of human diseases.

Of course it can sometimes be challenging to coordinate these different approaches or even translate the different languages that each expert speaks. One way to overcome these challenges for me is to permanently read publications in many different areas of research and communicate frequently with colleagues, if possible in person. Therefore it is sometimes easier to collaborate with researchers close by but fortunately modern electronic communication also enable collaborations across vast distances.

Do you have any ideas about where you will take your research next or will you need to wait for the results of your current research?

I am eager to expand our research on the connection between protein misfolding and aging. I find that this area of research is mostly unexplored and deserves more attention and innovative experimental initiatives, such as ours using yeast as a model.

Is there anything else you would like to add?

I lately observe with much concern that public opinion and many governments regard basic research as a rather wasteful and elitist pastime with little noticeable impact on our society. Yet it seems evident to me that basic research, which sometimes is not even directed towards a commercially measurable goal, will eventually help to solve humanities most pressing problems, including the dramatically growing number of people affected by neurodegenerative diseases. I therefore try to remind myself that as a researcher it my duty to share what we do and why we do it in an open dialogue.

Unravelling the Cellular Network

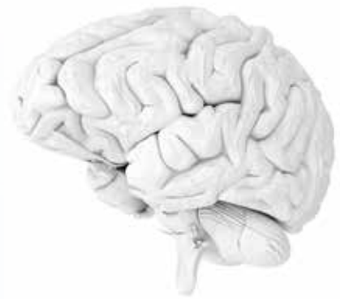
Protein misfolding is a key marker of many neurodegenerative diseases (ND) such as Huntington's disease (HD). Dr Martin Duennwald researches the underlying cellular mechanisms that result in protein misfolding, and therefore ND.

PROTEINS AND NEURODEGENERATIVE DISEASE

Proteins, like any molecule, must have a specific shape and size to function properly. Since proteins are very large molecules, specific shapes occur as a result of protein folding in which certain biochemical reactions within cells dictate how proteins are built. These reactions can be disrupted by a number of different factors, including toxic environmental substances, aging, and cellular energy production. These disruptions cause the proteins to fold into the wrong shape and size, and function improperly. Improperly functioning proteins can be toxic. In healthy humans, the cells in the body enact another set of biochemical reactions, called cellular stress programs, to counteract the damage. Proteins that have been made incorrectly will either be corrected or destroyed by the cellular stress programs. Neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and Huntington's disease are characterized by protein misfolding coupled with a failure of cellular response pathways to properly eradicate or correct protein misfolding. ND is one of the greatest health care burdens faced around the world today, as these diseases are often associated with aging and many countries will soon or already experience a growing elderly population. Duennwald's research is significant not only for the fundamental information it will generate, but also for its potential for developing new treatments for ND that may have a very direct, positive effect on society.

A COMPLEX DESIGN FOR A COMPLEX SUBJECT

Duennwald's proposed research ambitiously plans to explore protein folding from several different aspects. He uses an innovative approach that combines microscopic studies and cell biological experiments. He also studies cellular processes with transcriptome (RNA molecules), genome (DNA molecules), and proteome-wide studies. Proteome refers to the vast number of biological pathways that control how proteins are made and where they are sent within the cell. The data will be analysed using computational algorithms in order to discover the complex networks that result in protein misfolding.



It seems evident to me that basic research, which sometimes is not even directed towards a commercially measurable goal, will eventually help to solve humanity's most pressing problems, including the dramatically growing number of people affected by neurodegenerative diseases

To study protein misfolding in Huntington's disease (HD), Duennwald hypothesizes that the genetic mutation that causes HD significantly compromises the cellular stress programs of specific brain cells. Impaired cellular response in neurons would explain the brain damage seen in HD patients that contributes to the detrimental symptoms of HD. Therefore, Duennwald is focusing on HD mouse models and HD human brains to determine the role of stress response programs in the pathogenesis of HD. He will also evaluate whether targeting stress response programs can effectively be used as a treatment for HD.

In order to study the cellular mechanisms that cause protein misfolding, Duennwald used the heat shock response. This cellular stress program is activated by high temperatures that induce protein misfolding. The heat shock response can be induced by other conditions that result in protein misfolding, such as exposure to heavy metals and other environmental toxins. Much research has been conducted to determine the cellular processes involved in the heat shock response, which allows Duennwald to use it to study which biochemical reactions occur during protein misfolding in patients with ND. Research also demonstrates that the heat shock response may be linked to the development of many diseases and specifically ND. Duennwald would like to use this research to explore how the heat shock response differs between different types of tissues and cells, and figure out why cellular stress response programs fail in those cells afflicted with ND. This research will also help the medical community understand precisely how cells sense protein misfolding and activate the heat shock reponse. He also hopes this research will elucidate how aging affects the heat shock response.

Another significant aspect of Duennwald's study design is his choice to use yeast models to explore these cellular pathways. Yeast is cheap and easy to work with, saving both time and money. Yeast also grows quickly and is easy to manipulate and analyse in the laboratory. More importantly, the protein misfolding and cellular quality control programs Duennwald wishes to research are very similar between the yeast models and humans. Since it is both a simple organism and easy to manipulate, it is possible to conduct experiments that would be impossible using fruit flies, mice or humans. Yeast models allow the researchers to study the effects of entire genomes in rather simple experiments. Yeast can also be used as a living test tube to screen for molecules that may be further developed into treatments.

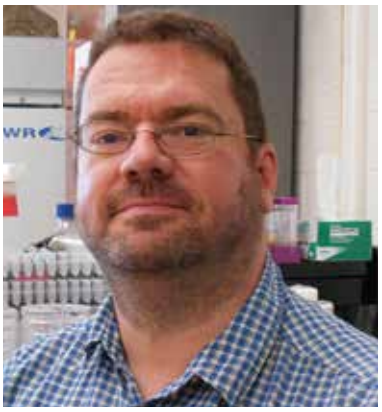
Duennwald also collaborates with other researchers, consulting biochemists and structural biologists to add insight regarding the molecular details of protein misfolding. He works with researchers who have expertise studying mouse models of neurodegenerative diseases, since they have a deep understanding of how particular neurons in the brain are involved in protein misfolding diseases. Finally, pathologists help validate the findings for human conditions.

WIDE-REACHING RESULTS

Duennwald hopes that his research methods will be applied to other diseases, such as cancer, diabetes and cardio-vascular disease. Protein misfolding is a hallmark of these diseases as well. This means that cellular stress programs may be similarly failing to correct or destroy misfolded proteins in these diseases. Duennwald's experimental tools will also elucidate why certain tissues and cell-types are affected in one disease, but not others. For instance, those suffering from cardio-vascular disease experience protein misfolding in the heart and blood vessels, while those suffering from diabetes will experience it in a wide variety of tissues and organs related to metabolic disease. Interestingly, cancer results from the opposite problem, cellular stress programs are hyperactive in cancer, allowing cells to divide. An understanding of how cellular processes are disrupted by failing stress response programs may lead to better therapies for a wide range of very common diseases.

The possible application of these research methods to other diseases demonstrates an important belief of Duennwald's. While this research project, specifically, does have the potential to generate money by creating intellectual property or through collaboration with bio-tech companies to provide jobs and lessen the burden of ND on the Canadian population through new treatment programs, this research is important for its own sake. It is often the case in scientific research that the outcome of any given research project may not produce results that are immediately economically viable or even applicable in real-life scenarios. However, since all research builds on past information, any seemingly impractical results will lead to better research in the future by providing information about the fundamental processes that shape the natural world. In this case, even if these new experimental tools do not prove to be useful for treating ND, researchers will have a deeper understanding of these diseases and new experimental tools to apply to other ailments. By focusing his research at the systems-level, Duennwald is contributing very important, fundamental information to the medical research community and may positively affect the lives of millions of people.

Researcher Profile



Dr Martin L. Duennwald
Department of Pathology
Schulich School of Medicine and Dentistry

Dr Martin Duennwald received his education from the Max-Planck-Institute for Breeding Research and the University of Cologne in Germany. He was awarded with a postdoctoral fellowship from both the German Research Association and the Huntington's Disease Society of America, and received an award on a talk about protein folding at the Federation of American Societies for Experimental Biology conference. He currently teaches at the Schulich School of Medicine and Dentistry where he researches protein misfolding, protein aggregation, neurodegenerative diseases, cellular protein quality control, protein-protein interactions and yeast models.

CONTACT

E: martin.duennwald@schulich.uwo.ca
T: (519) 661-2111 ext. 86874
W: http://www.schulich.uwo.ca/pathol/people/bios/faculty/duennwald_martin.html

COLLABORATORS

Gary Shaw PhD, Western University
James Shorter, PhD, University of Pennsylvania
Michael Strong, MD, Western University

FUNDING

CIHR
Parkinson's Society of Canada
ALS Society of Canada
Hereditary Disease Foundation
American Federation for Aging Research

Schulich MEDICINE & DENTISTRY