The Mammalian Proprotein Convertases in Health and Disease: Translational Clinical Applications in Cardiovascular Diseases, Cancer and beyond

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Abstract:
In the 1960s it was realized that many active proteins and peptides are generated following cleavage of their inactive precursor forms (proproteins) by proteolysis at single or pairs of basic residues. The long search for the cognate secretory proteases called "proprotein convertases" finally led in 1990-2003 to the molecular identification of a family of 9 mammalian serine proteases related to bacterial subtilisin and yeast kexin (PCSKs). The first seven members PCSK1-PCSK7 are basic amino-acid-specific convertases that cleave their substrates after the general motif (**R/K**)-2Xn-**R**↓, and the other two members PCSK8 and PCSK9 are activated following cleavage at non-basic residues. Studies of the physiological and pathological functions of the PCSKs revealed their implications in health and disease in humans, animal models, and in the activation of multiple infectious organisms. These include hormones, growth factors and their receptors, enzymes, membrane-bound transcription factors, as well as pathogenic viruses and bacteria. While PCSKs are at the crossroads of many pathways leading to disease, therapeutically targeting them is challenging. The success of the strategies used, and the inhibitors/silencers chosen depends heavily on the safety and efficacy of these compounds, and the absence of deleterious off-target side effects.
In that context we have recently concentrated on two convertases PCSK9 and PCSK7 that act non-enzymatically and of which inhibition/silencing hold enormous potential for the treatment of hypercholesterolemia, lipid disorders, inflammation and cancers with their associated metastasis. Inhibitors/silencers of PCSK9 are now prescribed clinically worldwide in more than 90 countries to reduce the levels of human LDL-cholesterol, the development of atherosclerosis and the incidence of myocardial infarction. PCSK9 inhibitors also enhance the levels of the cell surface Major Histocompatibility Complex class I and II (MHC-I and MHC-II) proteins, thereby enabling the immune system to better identify and eliminate cells that are cancerous or those infected by viruses. Recently, we discovered a novel method to potentially enhance the efficacy of immunotherapies used to treat a variety of cancers, including metastatic solid tumors, which account for > 90% of all cancer-related deaths. Our data revealed that PCSK7 can also exert chaperone-like functions on multiple immune checkpoint proteins (ICPs) in $CD8^+$ and $CD4^+$ T cells in mice and human. We observed that silencing *Pcsk7* expression in mice protects against colon and pancreatic carcinoma, even more so when combined with *Pcsk9* deletion. Thus, a novel mechanism was uncovered whereby the lack of PCSK7 enhances T-cells cytotoxicity by reducing the cell-surface levels of multiple ICPs. This was confirmed in primary human T-cells lacking PCSK7 expression using CRISPR-cas9 silencing, providing a realistic path towards clinical translation of such findings into cancer immunotherapy. Cumulatively, our data provide a *PCSK7*-silencing strategy to reduce the levels of cell-surface ICPs, thereby rationalizing the use of *PCSK7*-silencers in T-cell immunotherapies alone, or in combination with a PCSK9 inhibitor/silencer that enhances the levels of MHC-I and those of active T-cell receptors (TCR).

Biography:

Dr. Seidah obtained his BSc in 1969 from Cairo University in Egypt, and his PhD in 1973 from Georgetown University, USA. In 1974, he started studying the processing of precursor proteins at the Montreal Clinical Research Institute (IRCM), and in 1976 he co-discovered the β-endorphin and largely contributed to the biochemical characterization of the proopiomelanocortin (POMC, the β-endorphin precursor) and pro-Atrial Natriuretic factor. Since 1983, Dr Seidah is the director of Laboratory of Biochemical Neuroendocrinology. Dr. Seidah discovered and cloned seven (PC1, PC2, Furin, PC4, PC5, PACE4, PC7, SKI-1 and PCSK9) of the nine known secretory serine proteases belonging to the proprotein convertases family. During this period, he also greatly contributed to demonstrating that proteolysis by the proprotein convertases is a widely used mechanism that also affects "non-neuropeptide" proteins such as growth factors, α-integrins, receptors, enzymes, membrane-bound transcription factors, and bacterial and viral proteins. In 2003, he identified PCSK9 and showed that point mutations in the PCSK9 gene cause dominant familial hypercholesterolemia, since PCSK9 gain-of-function mutations were linked to the ability of PCSK9 to enhance the degradation of cell surface receptors, such as the low-density lipoprotein receptor (LDLR). Dr Seidah has since worked on the elucidation of the functions and mechanisms of action of PCSK9 both in cells and *in vivo*, and is developing specific PCSK9 inhibitors. Over the last 49 years, Dr. Seidah has attracted more than 150 graduate students, trainees and post-doctoral fellows. He is a member of numerous scientific associations including the Cancer Research Society and the American Heart Association. In 1991, he was elected fellow of the Royal Society of Canada. Dr Seidah is the recipient of several awards, including the 1995 Medical Research Council Scientist Award, he has been a member of the Order of Quebec since 1997 and of the Order of Canada since 1999. In 2001, he received the McLaughlin Medal of the Royal Society of Canada and the Parizeau Prize of the Association Canadienne-Française pour l'Avancement des Sciences (ACFAS). Since 2003 Dr Seidah has been endowed with a Tier-1 Canada chair on "Precursor Proteolysis". In 2009 he received the Pfizer Distinguished Cardiovascular-Metabolic Research Jean-Davignon Award. In 2011, he was awarded the Wilder Penfield prize for the best scientist in Québec working in the biomedical field.

In 2013, he was awarded the Queen Elizabeth II Diamond Jubilee Medal. In 2014, he received in Winnipeg the "Jacques Genest" Lecturer Award from the Canadian Society of Endocrinolgy and Metabolism. In 2016, he was selected as the recipient of the annual CIHR-ICRH Distinguished Lecturer Award in Cardiovascular Sciences in Canada. In 2018, he was selected for the prestigious Akira Endo Award for his seminal contributions to PCSK9 that led to a new powerful treatment for atherosclerosis, In 2018, he was granted the major Lefoulon Delalande award of the Institut de France for Research & Innovation in cardiovascular disease, and in 2019 the McGill University Louis & Artur Lucian award for research in circulatory diseases. In 2021, he was elected Fellow of the Canadian Academy of Health Sciences (FCAHS) and was selected for the KUWAIT 2021 prize (KFAS) honoring medical research scientists of Arab descent. In 2022 he gave a keynote lecture on the discovery of PCSK9 at the 15th international PCSK9 Forum. In 2023, he was elected "lifetime member" of the International Proteolysis Society. Additionally, his research lab received the prestigious "Bravo Recherche" Distinction from the Dean of the Medical Faculty at the University of Montreal, affirming their outstanding work supported by a UdeM-backed Canada Chair. The same year, Dr. Seidah's pioneering efforts in medicine were acknowledged with the esteemed J. Allyn Taylor International Prize for Medicine, specifically for his groundbreaking work on biotherapeutics for cardiovascular disease. In 2024, Dr. Seidah received congratulations from the Vice-Dean of the Medical Faculty at UdeM for achieving the top rank in the CIHR grant, showcasing the excellence of his project titled "The unique and complementary functions of PCSK7 and PCSK9 in cardiometabolic health and disease." He has been invited as a speaker nationally and internationally to give more than 490 presentations, and 32 plenary lectures worldwide. In 1995, he organized the first Keystone conference on proprotein convertases. In 2006 he was the

chairman of a prestigious Gordon Research Conference on "Proprotein Processing, Trafficking and Secretion" (Colby Sawyer College, NH, USA). In 2013 he was invited to present the “Simon Pierre-Noël Memorial Lecture” at the Canadian Lipoprotein Conference in Mont-Tremblant, Québec, Canada. In 2018 and 2019, he delivered keynote lectures for the “Akira Endo” and “Louis & Artur Lucian” awards on the discovery and clinical applications of PCSK9. In 2023 was Keynote Lifetime Achievement Lecture titled "The pluripotent proprotein-convertases: from fundamental biology to disease treatments" at the 12th General Meeting of the International Proteolysis Society in Singapore. He then discussed "The unexpected twists and turns of the proprotein convertases and their targeting in cardiovascular diseases and cancer/metastasis" at the CBR seminar series in Canada. He was also invited to give a talks at McGill University and McGill University Health Centre, addressing the pluripotent nature of proprotein-convertases and their implications in major pathologies. He presented a plenary lecture for the J. Allyn Taylor International Prize in Medicine and give an insightful presentation on "Roles of the proprotein convertases in health and disease" at the University of Virginia's UVA Comprehensive Cancer Center. Dr Seidah is an internationally recognized world leader in convertases and their physiological roles. His numerous publications, tallying more than 810 peer reviewed manuscripts, are widely recognized, and in fact he is cited as the most recognized protease expert in Canada and 6th worldwide. Indeed, Pubmed cites N.G. Seidah as the topmost in Canada and the 1st out of the worldwide 20 top scientists working on “Proprotein Convertases” since 1971. His H index = 119 (*Web of Science*; all databases) and 131 (*Google Scholar*), and his work has been cited more than 70,000 times.