One group of enzymes could have a positive impact on health, from cholesterol to osteoporosis

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Recent studies conducted at the Institut de recherches cliniques de Montréal (IRCM) on a group of PCSK enzymes could have a positive impact on health, from cholesterol to osteoporosis. A team led by Dr. Nabil G. Seidah, Director of the Biochemical Neuroendocrinology research unit, has published six articles in prestigious scientific journals over the past four months, all shedding light on novel functions of certain PCSK enzymes.

PCSK enzymes belong to the proprotein convertase family, responsible for the conversion of an inactive protein into its active state. The latest projects led by Dr. Seidah and his team focused on five of the nine PCSK enzymes, which are implicated in diseases such as cardiovascular and neuroendocrine disorders, cancer, and viral infections.

PCSK9 could help lower bad cholesterol levels

A member of the proprotein convertase family, PCSK9 plays a key role in the regulation of cholesterol. It is involved in causing familial hypercholesterolemia, a genetic disorder characterized by high total cholesterol levels in the blood, specifically very high levels of LDL (low-density lipoprotein) or bad cholesterol, which can lead to the early onset of cardiovascular diseases. PCSK9 is thus a target for the treatment of dyslipidemia, which results from an abnormal concentration of lipids (fat) in the blood. It is believed that inhibition of PCSK9 function could

lower LDL-cholesterol levels, and such treatments are currently undergoing early phase clinical trials.

"Members of my team, led by Dr. Annik Prat and Dr. Anna Roubtsova, discovered that PCSK9 also regulates fatty acids," explains Dr. Seidah. "They investigated its role in the metabolism of body fat, and found that PCSK9 is pivotal in regulating cholesterol and fat metabolism: it maintains high circulating cholesterol levels, but it also limits fat generation."

In another study, the researchers uncovered further data on PCSK9's mechanism of action and functional structure. Their data showed that a part of PCSK9 inhibits its own function, and that acidic pH levels affect the degradation of bad cholesterol receptors.

In a third study, the team discovered that two other PCSK enzymes, Furin (PCSK3) and PC5/6 (PCSK5), reduce the level of active PCSK9. "They were able to demonstrate how enzymes of the PCSK family communicate with one another and found that liver-derived Furin cuts PCSK9 and inactivates it," adds Dr. Seidah. "This provided genetic evidence for the mechanism behind the functioning of a mutant gene found in some human hypercholesterolemic patients."

An important enzyme for osteoporosis, especially for women after menopause

The eighth member of the family (PCSK8), known as SKI-1/S1P, is critical in the intracellular pathway leading to the synthesis of cholesterol and fatty acids. Researchers discovered a new function of the enzyme in the regulation of bone formation. They demonstrated that mineralization – the process by which the body uses minerals to build bone structure – was blocked by inhibitors of SKI-1/S1P.

"The team found that SKI-1/S1P also regulates the activation of a membrane-bound transcription factor required for bone formation, which could have an impact on osteoporosis," says Dr. Seidah. "This could be especially important for women after menopause, as they are most likely to develop bone disease."

A better understanding of an enzyme implicated in various cancers

PC7 (or PCSK7) is the most ancient and highly-conserved basic amino acid-specific member of the proprotein convertase family. The team of researchers, led by Estelle Rousselet, shed light on how PC7 functions within cells, and was able to define its intracellular trafficking pathways. "We identified a mechanism for PC7's unique ability to activate the precursor of epidermal growth factor, which is involved in various cancers, tumour growth, and the maintenance of stem cells," concludes Dr. Seidah.

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