

The Centre for Blood Research presents

CBR SEMINAR SERIES



Wednesday, November 22, 2023
1:00PM - 2:00PM PT

Life Sciences Centre
1003 (LSC3) & Zoom

“The unexpected twists and turns of the proprotein convertases: targeting in cardiovascular diseases and cancer/metastasis”

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The mammalian proprotein convertases (PCs) constitute a family of nine secretory serine proteases related to bacterial subtilisin and yeast kexin. Seven of them (PC1/3, PC2, furin, PC4, PC5/6, PACE4 and PC7) activate cellular and pathogen precursor proteins by cleavage at single and/or paired basic residues in polypeptide hormones, growth factors and their receptors, adhesion molecules and enzymes / proteases. They are implicated in cancer / metastasis, inflammation and pathogen infections, including SARS-CoV-2. Of those enzymes, only PC7 (gene PCSK7) also exhibits non-protease activities as a chaperone for apolipoprotein B (apoB) and enhances the degradation of apolipoprotein A-V (apo A-V). PCSK7 inactivation was shown to result in ~50% reduction of liver / circulating apoB levels. Following fatty liver induction in mice to mimic the non-alcoholic fatty liver disease (NAFLD), liver PCSK7 inhibition (galactosamine-antisense oligonucleotides) demonstrated that PC7 represents a powerful new target for the treatment of this highly prevalent disease. The last member of the PC family, PCSK9 has no enzymatic activity in trans, but enhances the endosomal / lysosomal degradation of cell-surface receptors, such as the LDLR implicated in cholesterol / lipid homeostasis, MHC-I members that regulate CD8+ T-cell activities / iron homeostasis. Injectable / safe PCSK9 monoclonal antibodies (mAb) that reduce by ~60% the circulating LDL-cholesterol have been prescribed for the last 7 years. Moreover, PCSK9 mAb / siRNA are now tested as adjuvants to current immune- / chemo-therapies in cancer / metastasis. Finally, ectopic pancreatic tumor cells growth in Pcsk7 KO mice are drastically reduced compared to WT mice, implicating the activation of CD8+ T- cells and reduced cell surface levels of checkpoint inhibitors. Unsuspected additional roles for the multifunctional convertases may be uncovered in the future, likely opening the door to novel clinical applications of their inhibitors / silencers.

Many thanks to
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