ENGINEERING HONORS PROGRAM
UNIVERSITY OF MICHIGAN

BIOMEDICAL ENGINEERING
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Reprogramming of Steroid Metabolism in Natural Killer Cell Activation via Lipids

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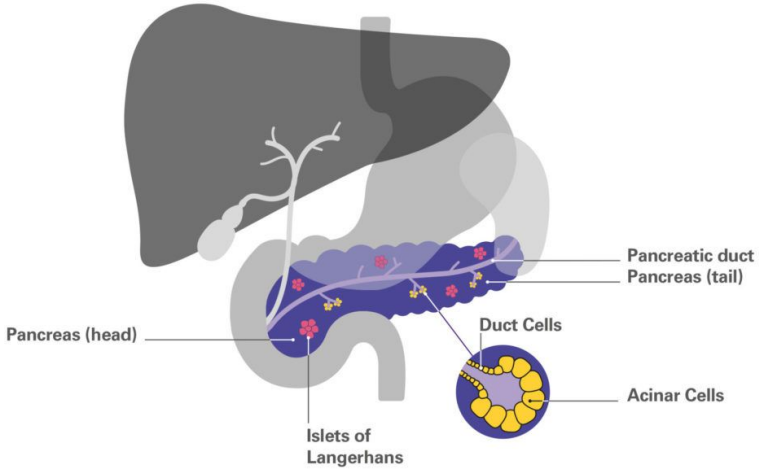
Agenda

- Background
- Objectives
- Results
- Conclusions
- Future Directions

Background

- Pancreatic ductal adenocarcinoma (PDAC) is a type of pancreatic cancer that is extremely lethal and essentially untreatable
  - Accounts for 90% of all pancreatic cancer cases [1]
- 5 year survival rate of only 6% [2]



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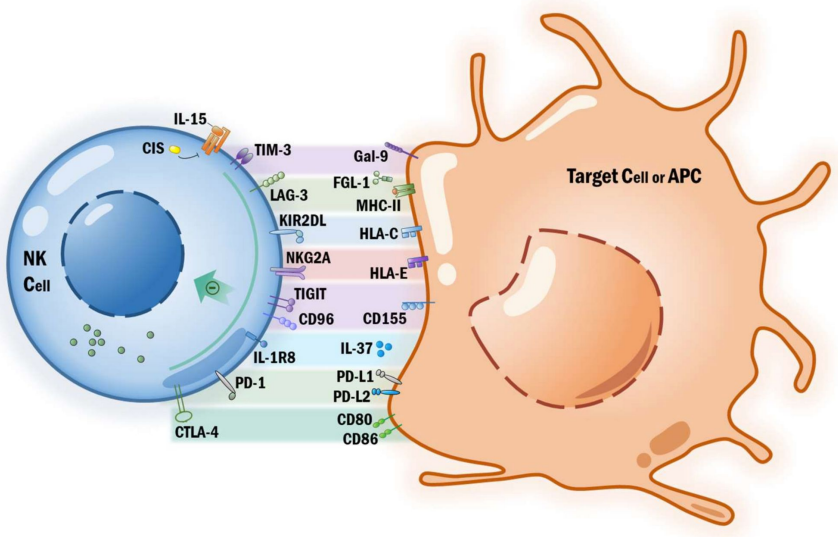
Background

- Natural Killer (NK) cells are an important part of the innate immune system
  - Innately monitor and kill cancer cells
- Understanding metabolic requirements can help them become more effective at fighting PDAC



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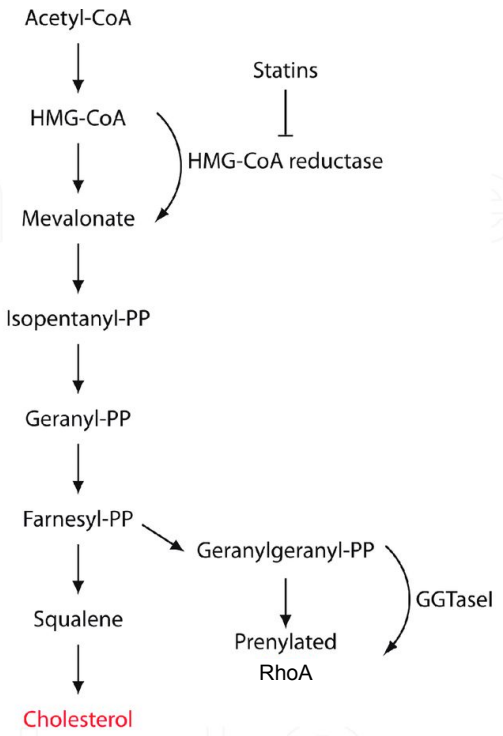
Background

- NK cells use a reprogrammed metabolism based on SREBP2
  - SREBP2: master regulator of sterol and fatty acid synthesis
- Statins lower cholesterol levels in the body
- Steroids are synthesized via the mevalonate pathway
  - Building block: acetyl-CoA from glucose
  - Protein prenylation



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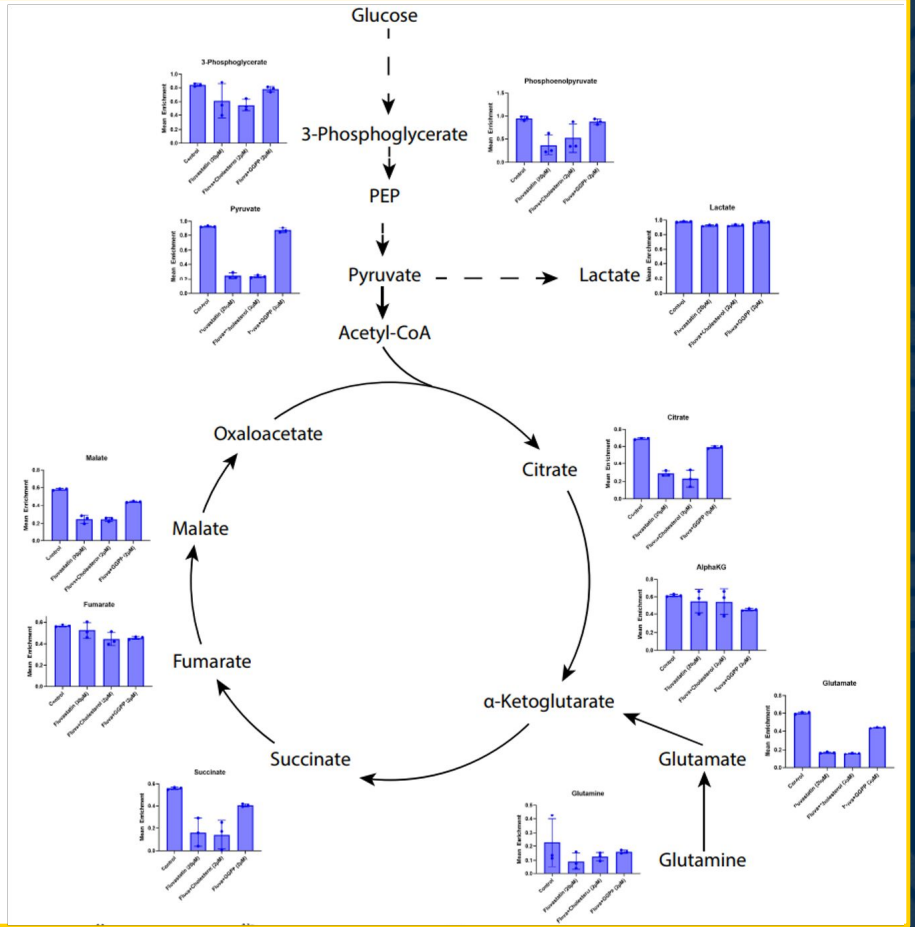
Objectives

1. Determine the metabolic requirements of NK cells for mevalonate pathway

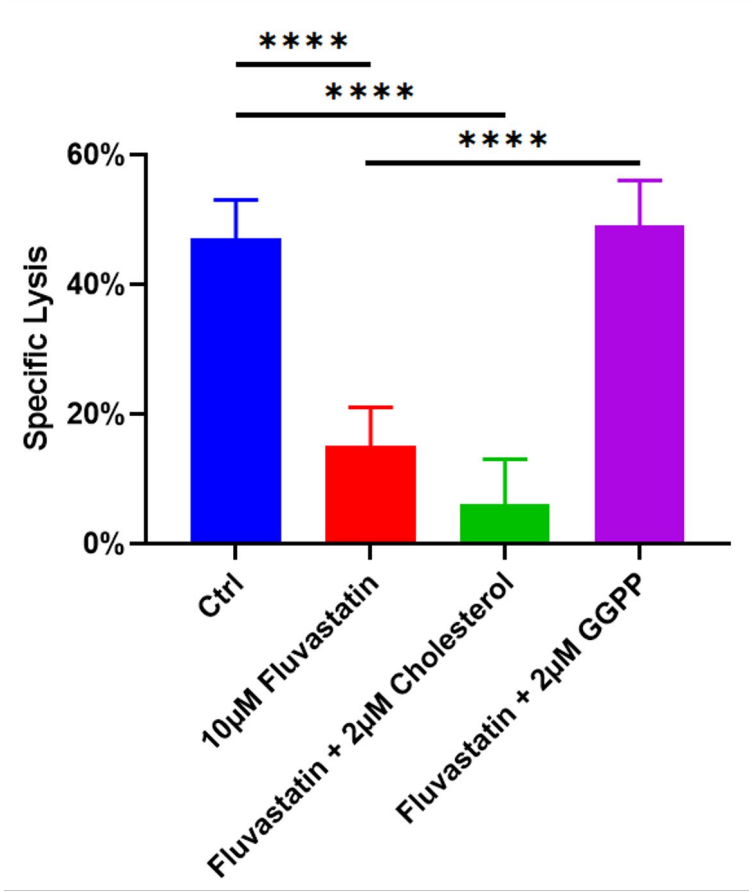
2. Understand how protein prenylation regulates NK cell activity

3. Investigate how peroxisomes, which metabolize unsaturated fatty acids, relate to cholesterol metabolism

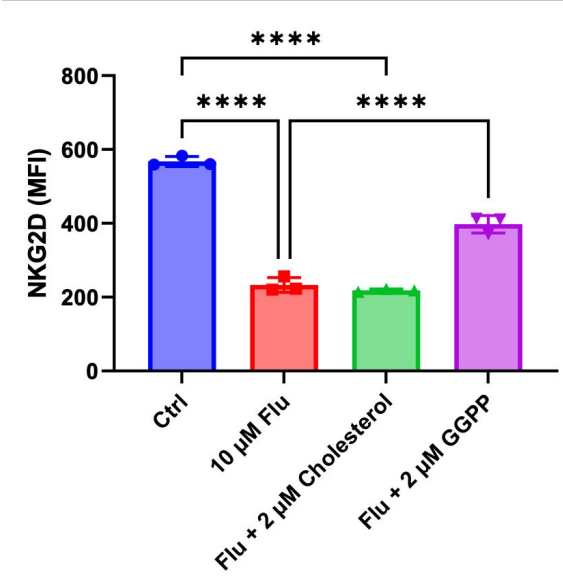
Glucose metabolism is altered by statin treatment in NK cells

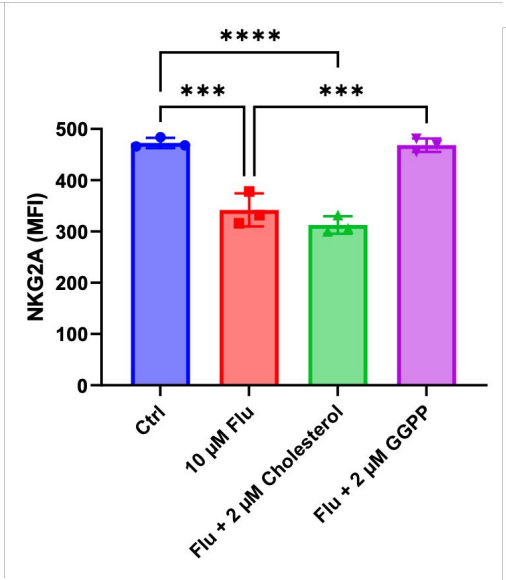


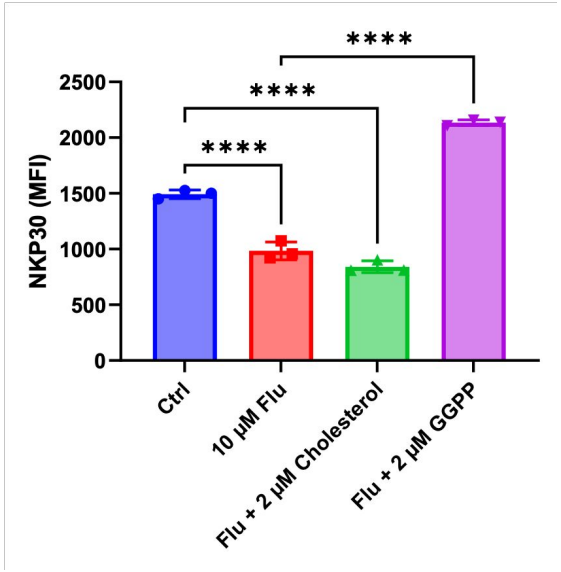
NK cells are dependent upon prenylation substrates for cytotoxicity



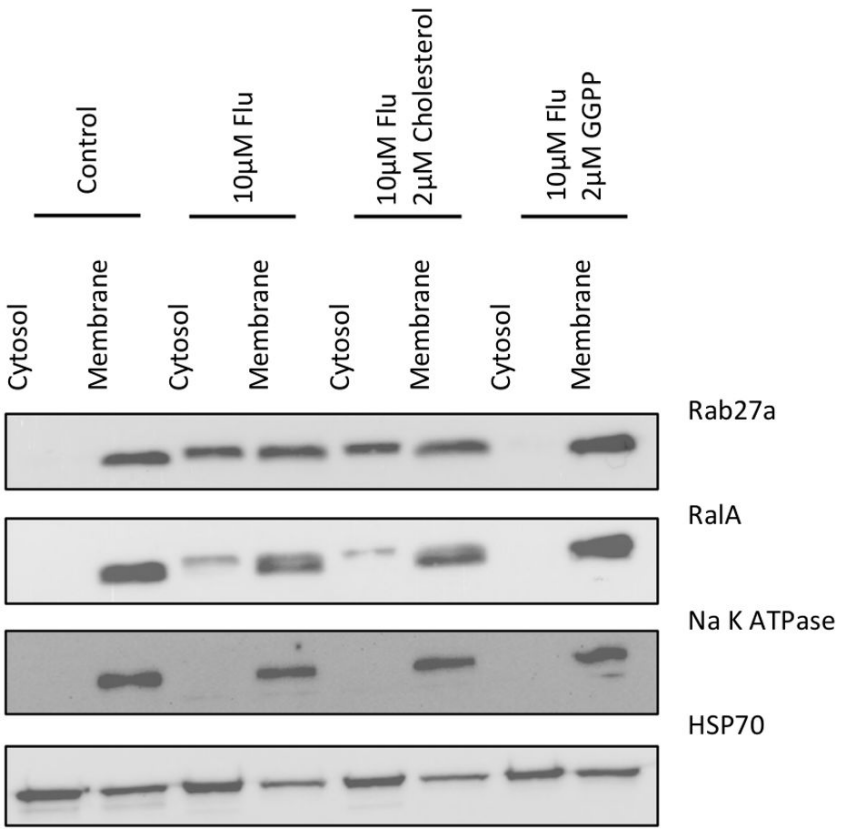
NK cell surface markers are downregulated by statin treatment and rescued by prenylation substrates



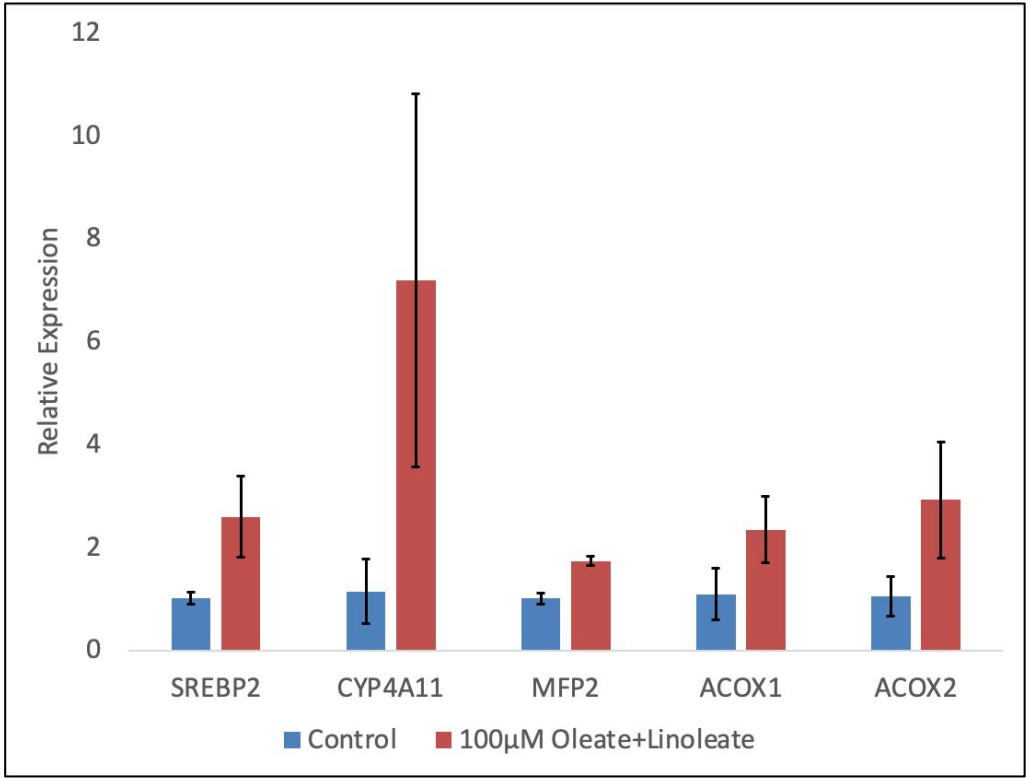




Statin treatment displaces vital trafficking proteins, affecting NK cell function



Lipids can regulate peroxisome and cholesterol metabolism genes



Conclusions

- Protein prenylation is vital for NK cell function
- NK cell function is determined by lipid metabolism
- GGPP treatment

Future Directions

- Investigate how peroxisomes connect NK lipid metabolism to cholesterol metabolism in the tumor microenvironment

Thank you for listening!

FAQ

How did you get involved in this project?

What inspired you?

How do you hope to use what you learned from this project in your future career?

References

[1] Sarantis, P., Koustas, E., Papadimitropoulou, A., Papavassiliou, A. G., & Karamouzis, M. V. (2020). Pancreatic ductal adenocarcinoma: Treatment hurdles, tumor microenvironment and immunotherapy. *World Journal of Gastrointestinal Oncology*, *12*(2), 173–181. https://doi.org/10.4251/wjgo.v12.i2.173
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