

Investigating the Biological function of proteins found in Mycobacteria in response to sterol exposure

Adrian Palumbo

Personal Background

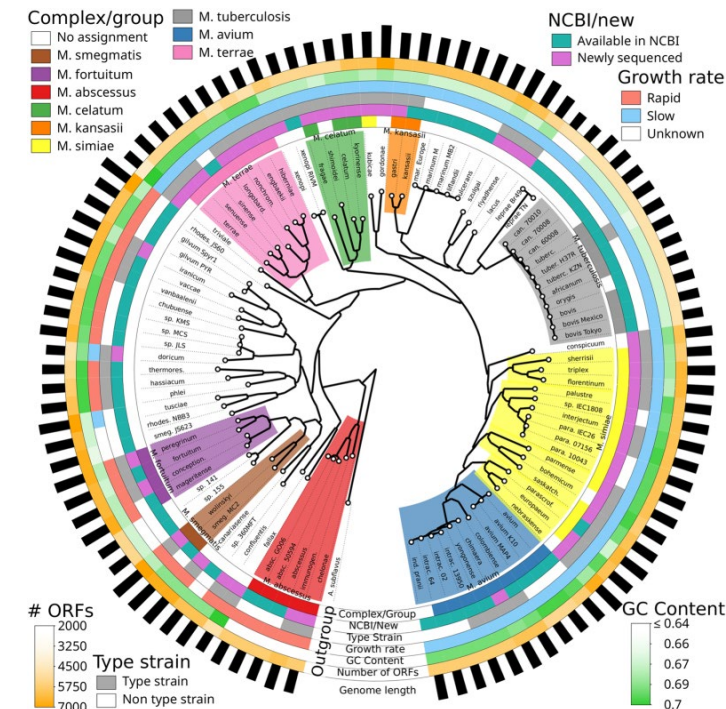
- 3rd year at Case Western Reserve University in Cleveland Ohio
- Double majoring in Biochemistry and Classics (Ancient Greek and Latin)
 - Plan to pursue a Ph.D in some bio-science field after graduation, in order to continue to work in science/research
- Research background
 - Worked at a Biotech Company making regenerative medicine out of amniotic materials, developed a freeze-dried product
 - Currently researching the protein trafficking of large ion channels in the CNS, and how to modulate these processes with drug compounds
- Outside of school, I sing in a band and with Case Glee Club, play volleyball, and volunteer at a local animal shelter

Research Project

Intro to Mycobacteria

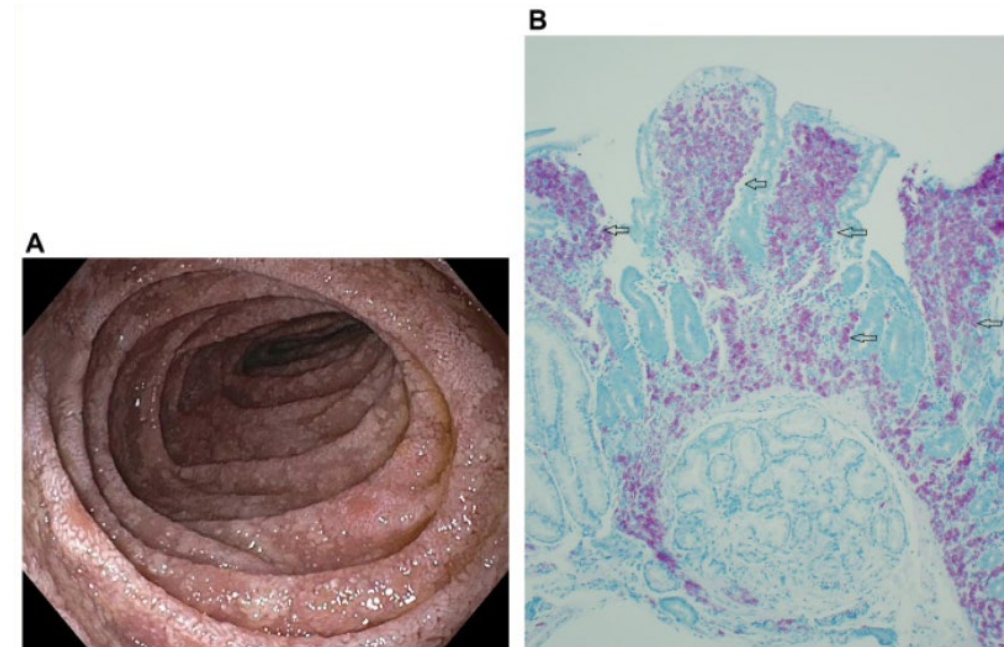
- Broad family of pathogens including *M. tuberculosis* and *M. leprae* (Leprosy)
- Some use host cholesterol as an energy source when infecting
- *M. avium* is a opportunistic pathogen, infecting immunocompromised patients
 - No straightforward treatment options

Fedrizzi, T., Meehan, C. J., Grottola, A., Giacobazzi, E., Fregni Serpini, G., Tagliacuzzi, S., Fabio, A., Bettua, C., Bertorelli, R., De Sanctis, V., Rumpianesi, F., Pecorari, M., Jousson, O., Tortoli, E., & Segata, N. (2017). Genomic characterization of Nontuberculous Mycobacteria. *Scientific reports*, 7, 45258.



Mycobacteria in the Gut

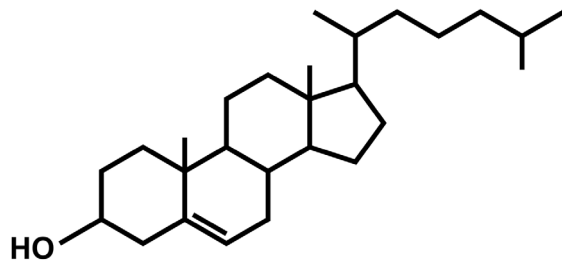
- Localize to gut environments despite adverse conditions
- Bile acids contribute to this, disrupt bacterial cell walls
- *M. avium* migrate towards the gut, and infect through the lining



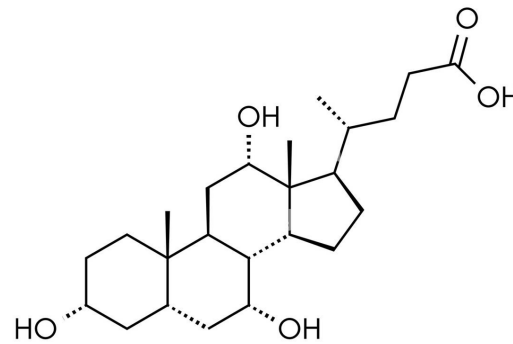
Bansal, R., Ayoub, M., & Policar, M. (2021). Gastrointestinal Mycobacterium Avium Complex. *The American journal of the medical sciences*, 361(3), e31–e32.

Sterols

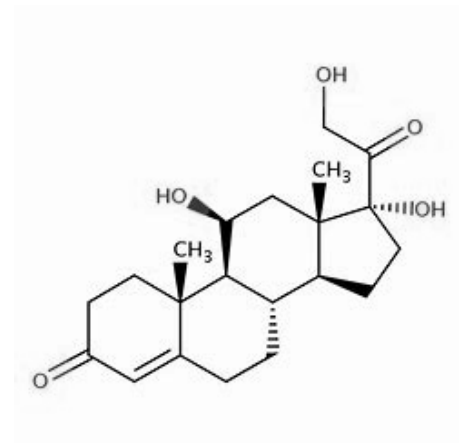
- Diverse class of molecules around a similar ring-backbone including cholesterol, bile acids, and steroid-based medications



Cholesterol



Cholic Acid



Hydrocortisone

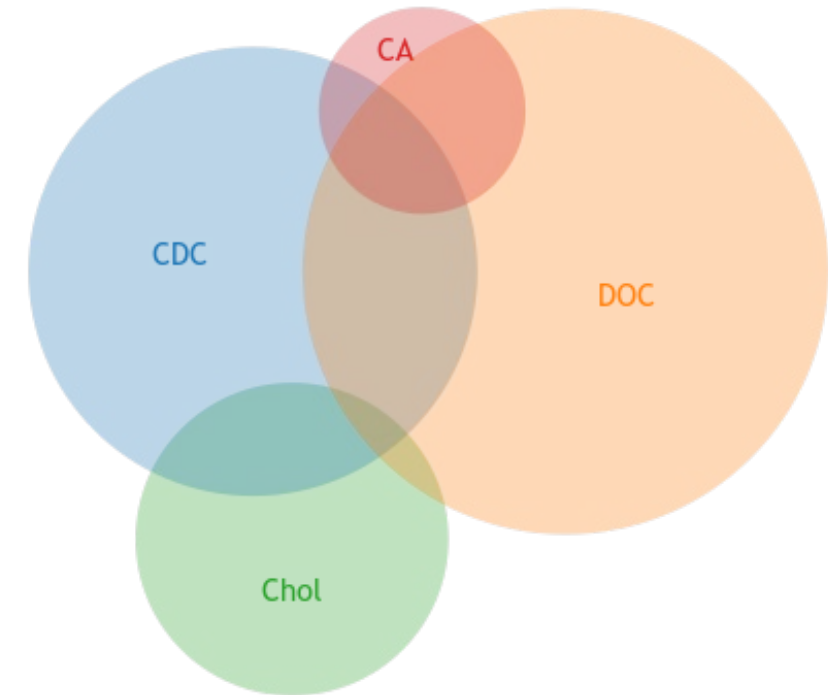
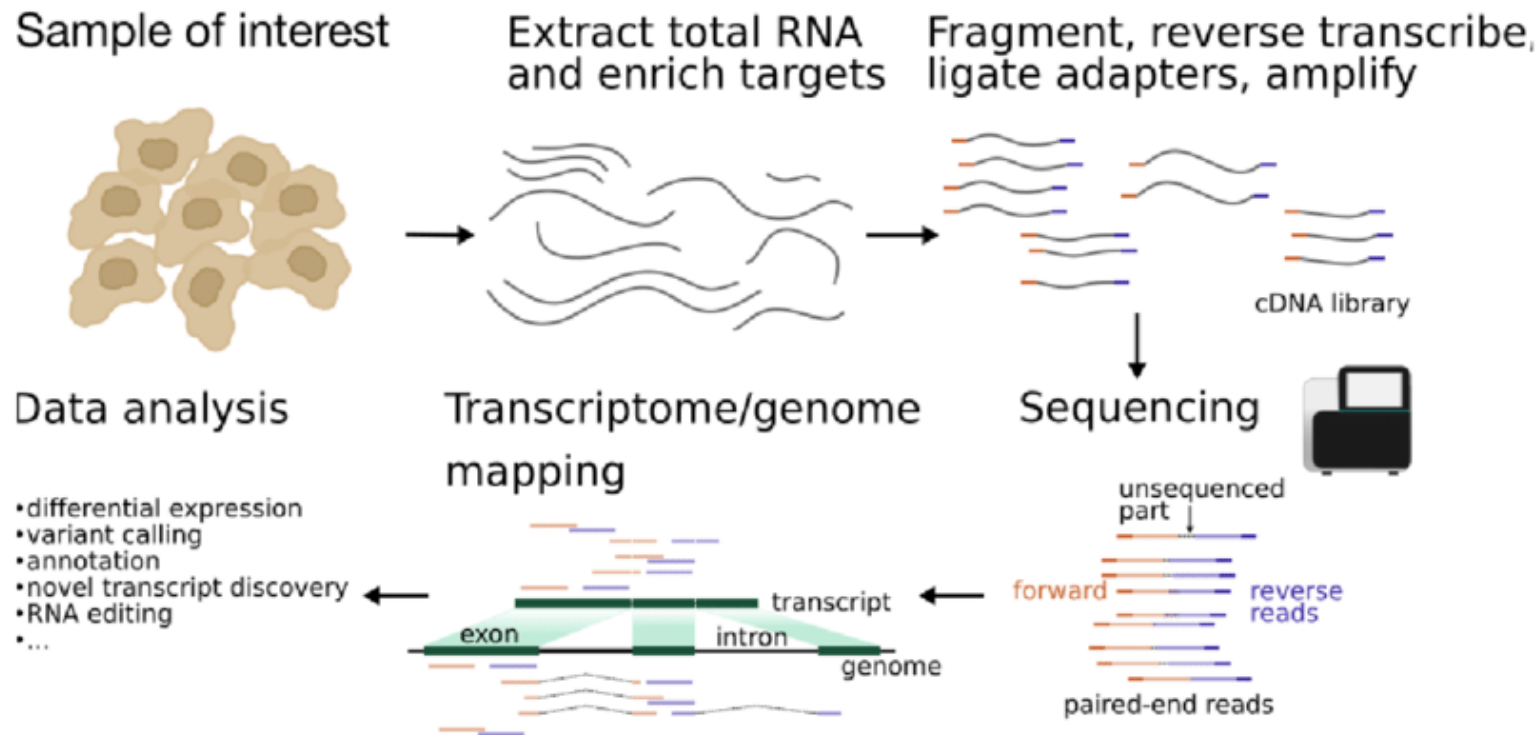
Central Question

It has been shown that cholesterol not only serves as an energy source for infectious mycobacteria, but also causes the expression of several proteins crucial for infection and survival in host systems. Could bile acids serve a similar purpose in infectious mycobacteria that localize to gut environments?

Applications

- Bacteria are the **ONLY** organisms that can break down sterols
- Potential for use in waste management, or more sustainable production of steroid-based medications
- Open up treatment options for currently poorly understood diseases

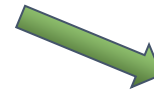
Brief Results-RNA Seq with Sterols



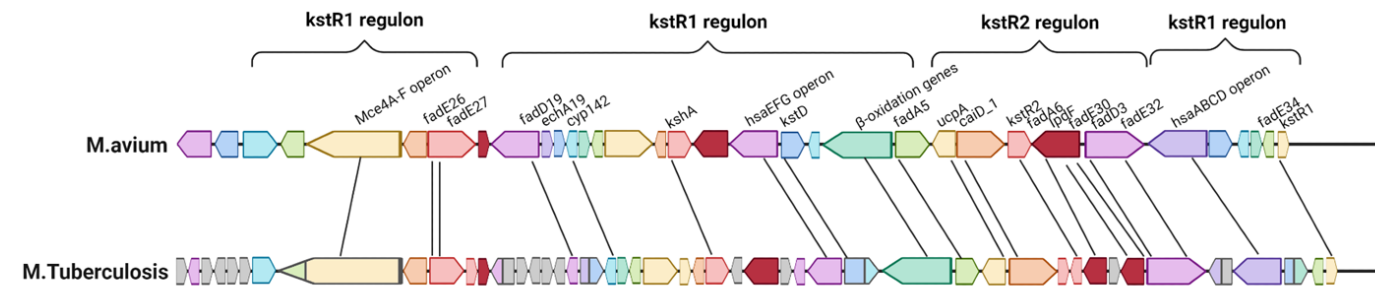
By ResearchGate

Gene Clusters

	CDC	DOC	CA	Chol	Genes	Notes
Cluster 1	█	█	█	█	87	Cholesterol metabolic cluster
Cluster 2	█	█	█		15	Universally upregulated across CA, CDC, and DOC
Cluster 3	█	█			29	Putative CDC metabolic cluster
Cluster 4	█	█	█		40	Putative DOC metabolic cluster
Negative-regulated cluster 2		█	█		5	
Negative-regulated cluster 3	█	█	█		10	
Negative-regulated cluster 4		█	█		15	
Negative-regulated cluster 5		█	█		8	
Negative-regulated cluster 6	█	█	█		7	
Negative-regulated cluster 7	█				33	
Small cluster 1	█	█	█		3	MmpL5
Small cluster 2	█	█	█		7	Regulatory Kinases
Small cluster 3	█	█	█		3	Seems to be involved in cell wall biogenesis
Small cluster 5	█	█	█		5	Panthetic Acid synthesis cluster
Small cluster 6	█	█			7	2-methyl citrate metabolism cluster
Small cluster 7	█				3	
Small cluster 8		█			3	
Small cluster 9	█	█			5	
Small cluster 10	█	█	█		6	Sterol Metabolism
Small cluster 11		█			3	
Small cluster 12		█			3	MmpL4 cluster
Small cluster 13	█	█	█		3	MmpL4 cluster
Small cluster 16		█			2	
Small cluster 20		█			3	
Small cluster 21	█	█			3	
Small cluster 22	█	█			3	
Small cluster 23	█	█			10	Very similar to urea cycle genes
Small cluster 25	█	█			8	Many mono-oxygenases, putative membrane association
Small cluster 30	█	█	█		2	Links to CoA metabolism
Small cluster 31		█			5	ACP-associated cluster
Small cluster 32		█			6	Beta-oxidation cluster
Small cluster 34		█			3	
Small cluster 37	█	█			4	
Small cluster 40		█			11	ribosomal proteins



Mycobacterial synteny of genes involved in cholesterol metabolism



Current Questions

- Can *M. avium*/other mycobacteria use bile acids as an energy source as they do with cholesterol?
- What are these smaller clusters involved in?
- Effect of sterol-associated membrane proteins on pathogenicity
- How are these molecules being imported into the cell and causing this transcriptional response?
 - Both on the transporter and regulator levels