European Crohn's and Colitis Organisation

Dysregulation of cell-type specific long ncRNA in the ileum of treatment naïve early onset Crohn Disease

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On behalf of the Crohn's & Colitis Foundation (CCF)-sponsored RISK study

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Disclosure of Conflicts of Interest:

Conflict of interest :

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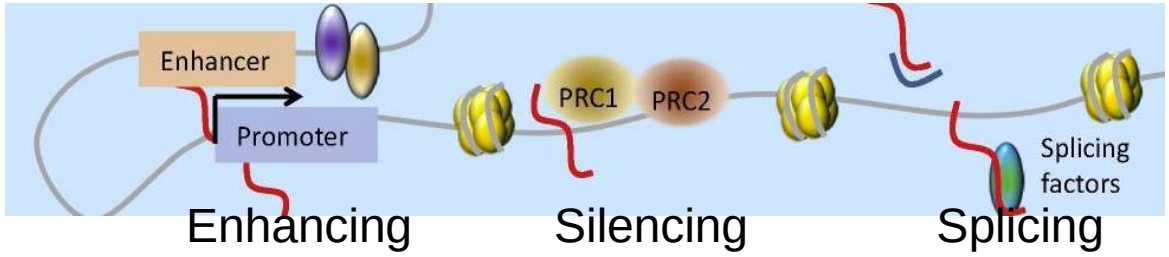
lncRNA definitions and known functions

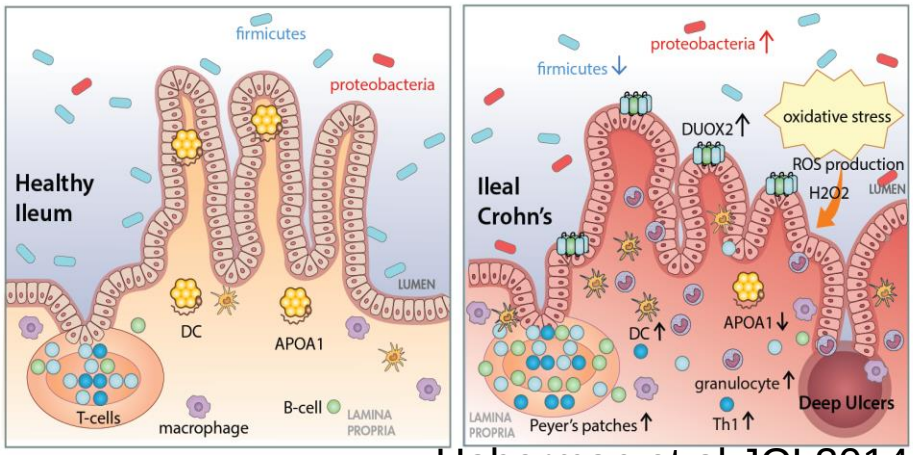
- LncRNA are diverse class of non-protein coding transcripts longer than 200 nucleotides.
- LncRNA are key regulators of gene transcription.



- LncRNAs dynamically regulate the immune system (i.e. Morrbid, Lethe, Lnc-DC) .
- Only a few studies to date have focused on lncRNA in human gut pathogenesis, and there have been no studies of the ileum of patients with Crohn Disease.

Hypothesis and aim

We defined core inflammatory and metabolic ileal gene signature in treatment naïve pediatric Crohn Disease (CD).



Haberman et al JCI 2014

Our hypothesis is that **lncRNA will have tissue specific regulatory role in tuning the inflammatory cascade and epithelial functions in CD pathogenesis**

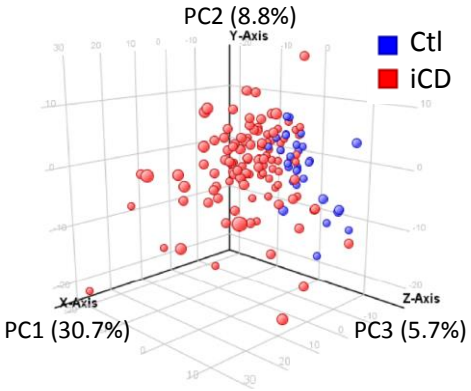
We extend our analyses to define a more comprehensive view of CD pathogenesis that includes lncRNA.

Widespread dysregulation of 459 lncRNA in the ileum of treatment naïve pediatric iCD (L1, L3) patients

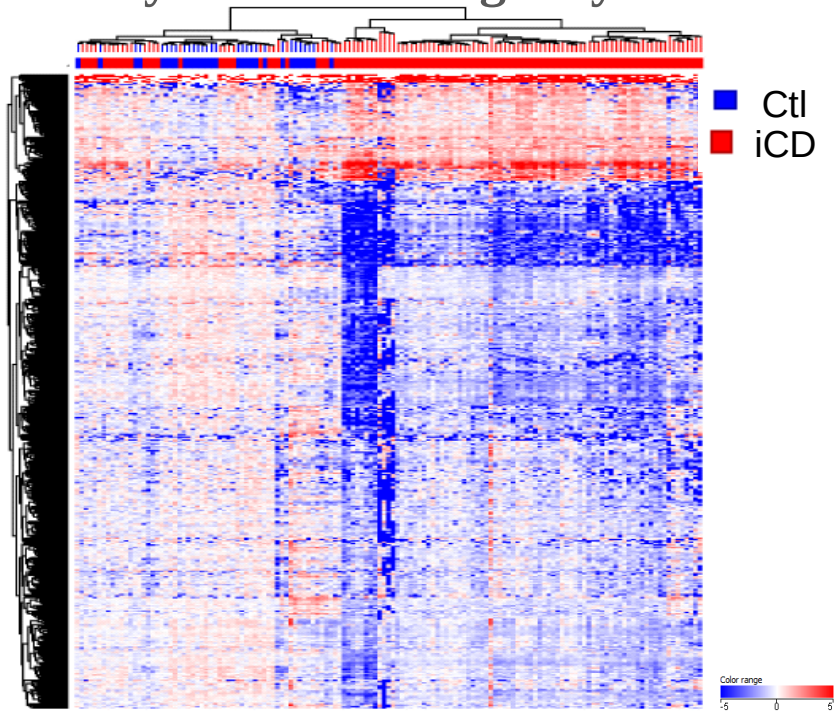
Discovery

	Ctl (n=30)	CD (n=111)
Age (mean, SD)	11.2(3)	11.9(3)
Male (%)	60%	61%
PCDAI mild (11-30)	-	39%
PCDAI mod-sev (>=31)	-	53%

Discovery cohort



Discovery cohort – using only lncRNA



LncRNAs can be utilized to correctly classify disease or healthy states

Haberman IBD J 2018

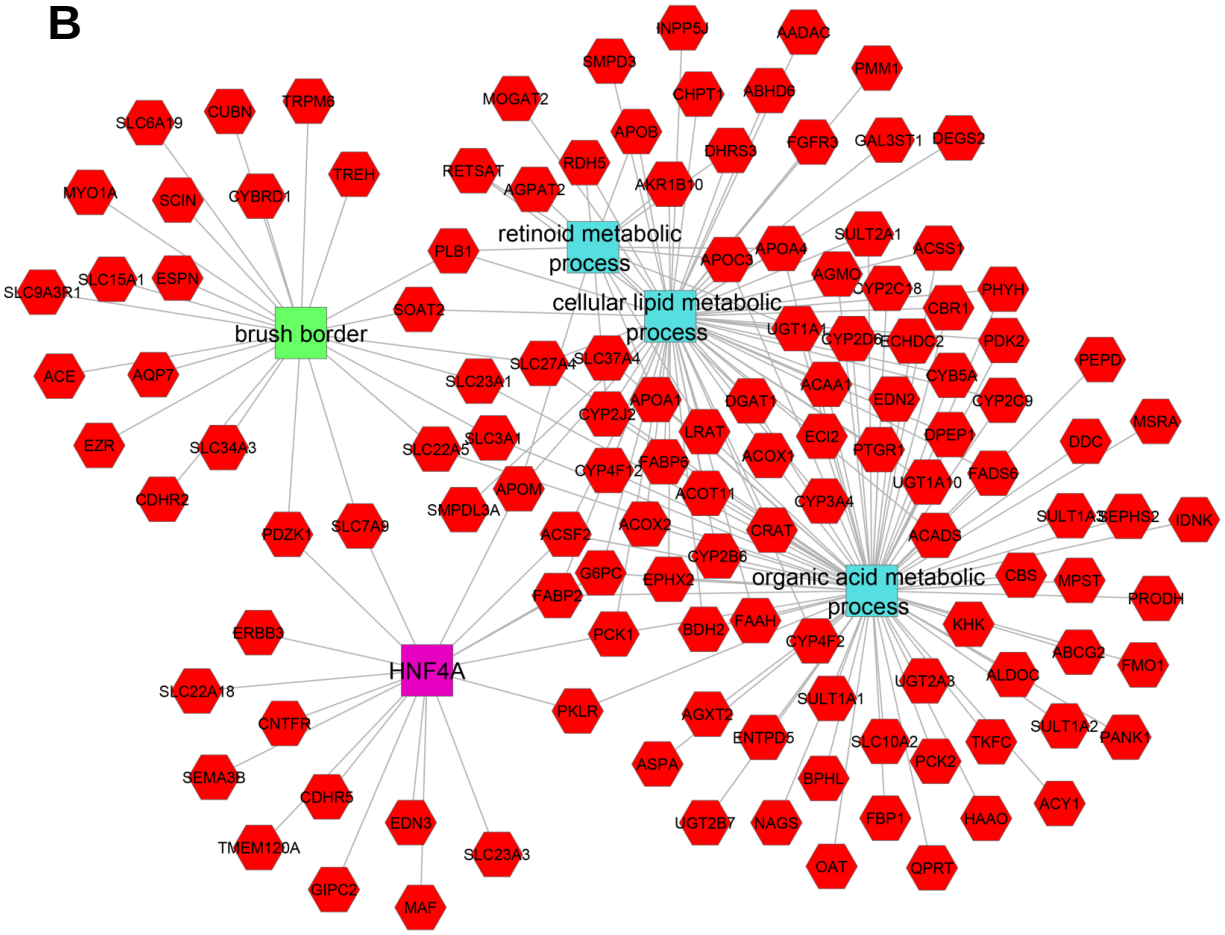
Prioritizing the down-regulated lncRNA based on fold change and by using "Guilt-by-association" co expression: top down-regulated *CDKN2B-AS1* (*ANRIL*) & HNF4A-AS1 lncRNAs show strong co-expression with an epithelial metabolic signature.

A

Top 15 down-regulated lncRNA genes

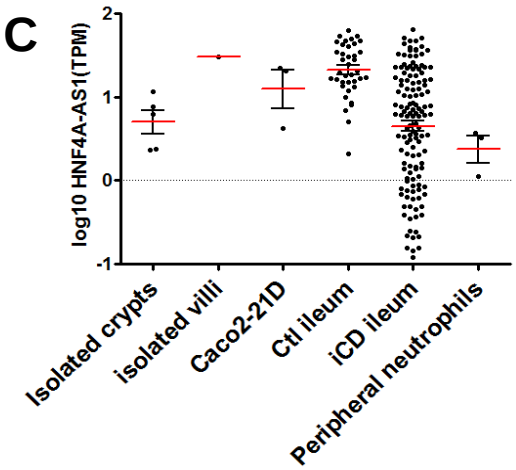
	FC (iCD] vs. [Ctl])	Co-expression
RP11-249C24.11	-16.2	1
RP11-347E10.1	-14.5	105
RP11-64D22.5	-8.5	6
FOXD1-AS1	-8.1	1
LINC01595	-7.9	1
RP11-132E11.2	-7.3	112
RP11-116D2.1	-7.0	25
CDKN2B-AS1	-6.9	365
RP11-245G13.2	-6.7	1
RP11-1223D19.1	-6.2	1
HNF4A-AS1	-5.9	315
RP11-798K3.2	-5.7	153
RP11-680F8.1	-5.6	73
RP3-368B9.2	-5.6	2
RP11-689K5.3	-5.5	1

B



CDKN2B-AS1 "Guilt-by-association" network

C

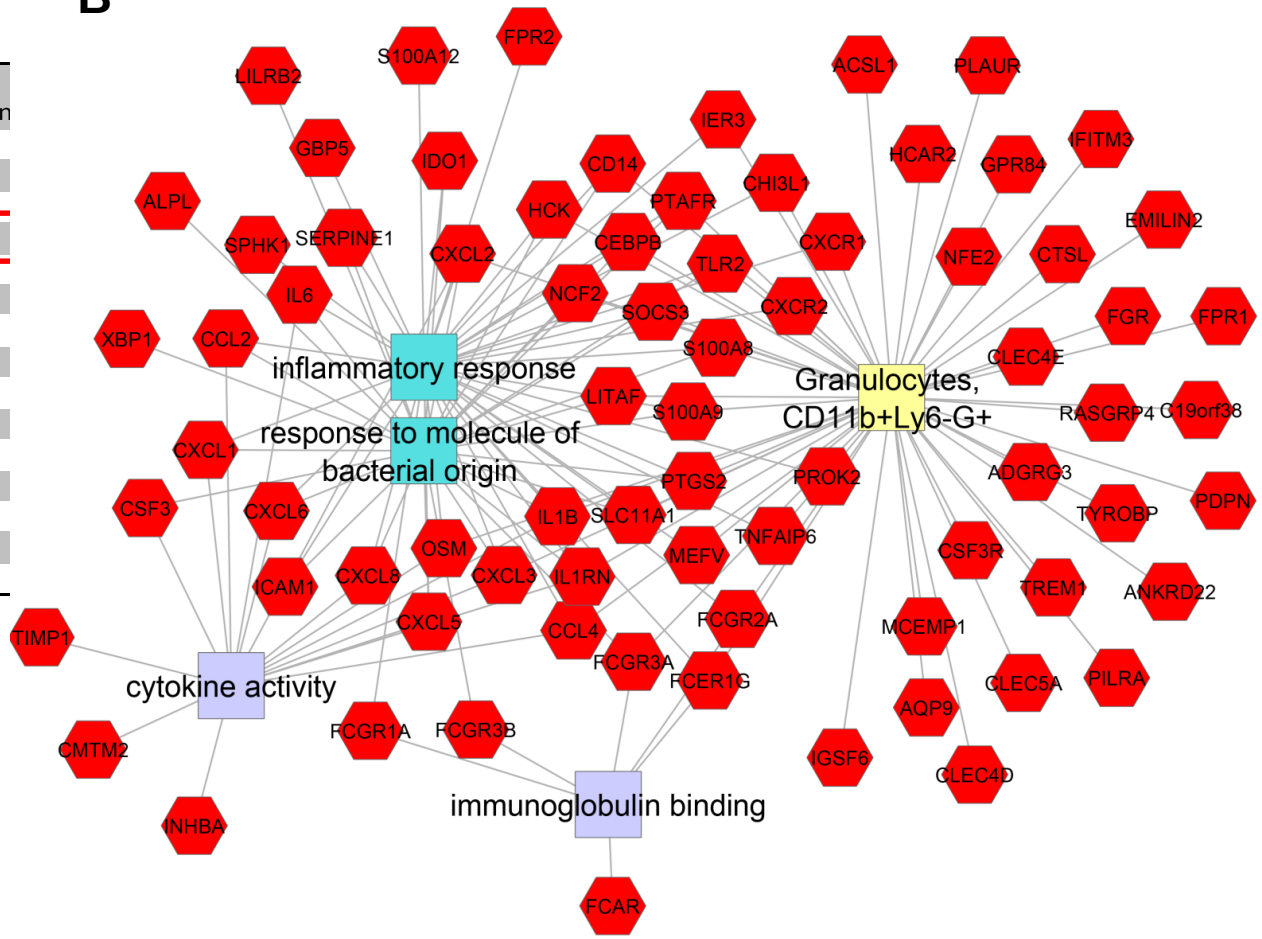


Prioritizing the up-regulated lncRNA based on fold change and by using **"Guilt-by-association" co expression:** the up-regulated LINC01272 is associated with a strong granulocytes signature

A

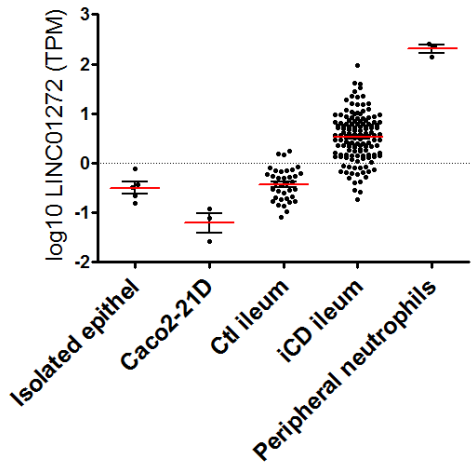
Top15 up-regulated differentially expressed lncRNA genes	FC [iCD] vs. [Ctl]	Co-expression
CTB-61M7.2	12.8	19
RP11-598F7.3	11.5	1
LUCAT1	10.8	17
LINC01272	9.3	116
RP11-290L1.3	7.1	1
LINC00694	6.4	1
CTC-490G23.2	5.9	1
RP11-701P16.5	5.8	1
LINC01235	5.2	1
RP11-638I2.8	4.9	1
FAM225A	4.4	46
RP11-44K6.2	4.4	1
RP11-20G13.2	4.2	1
RP11-536O18.1	3.7	1
CTA-384D8.35	3.6	1

B

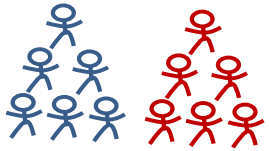


LINC01272 "Guilt-by-association" network

C



Conclusions and Future Considerations



Crohn Disease and controls Ileal samples

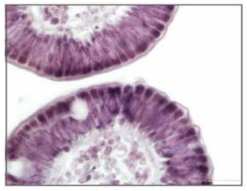
Differential expression using RNAseq and GENCODE/Ensembl annotation

2160 protein coding

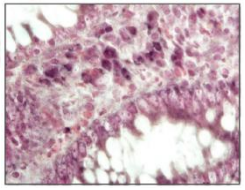
459 long non-coding RNA (lncRNA)

Equally and accurately classify Crohn Disease and control samples

Prioritization of lncRNA based on fold change and co-expression networks



Down-regulated lncRNa (i.e. HNF4A-AS1) show epithelial-specific expression and associations with metabolic functions



Up-regulated lncRNA (i.e. *LINC01272*) show specific myeloid expression and association with myeloid immune activation

We plan to elucidate their molecular mechanisms to provide more comprehensive insights into CD pathogenesis and ultimately lead to novel tissue specific therapies

Acknowledgments

Sheba Medical center

Lab members

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- Ayelet Di segni*
- Gilat Efroni
- Marina BenShoshan*
- Nurit Nachum
- Katia Sosnovski

Collaborators:

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RISK cohort site investigators

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