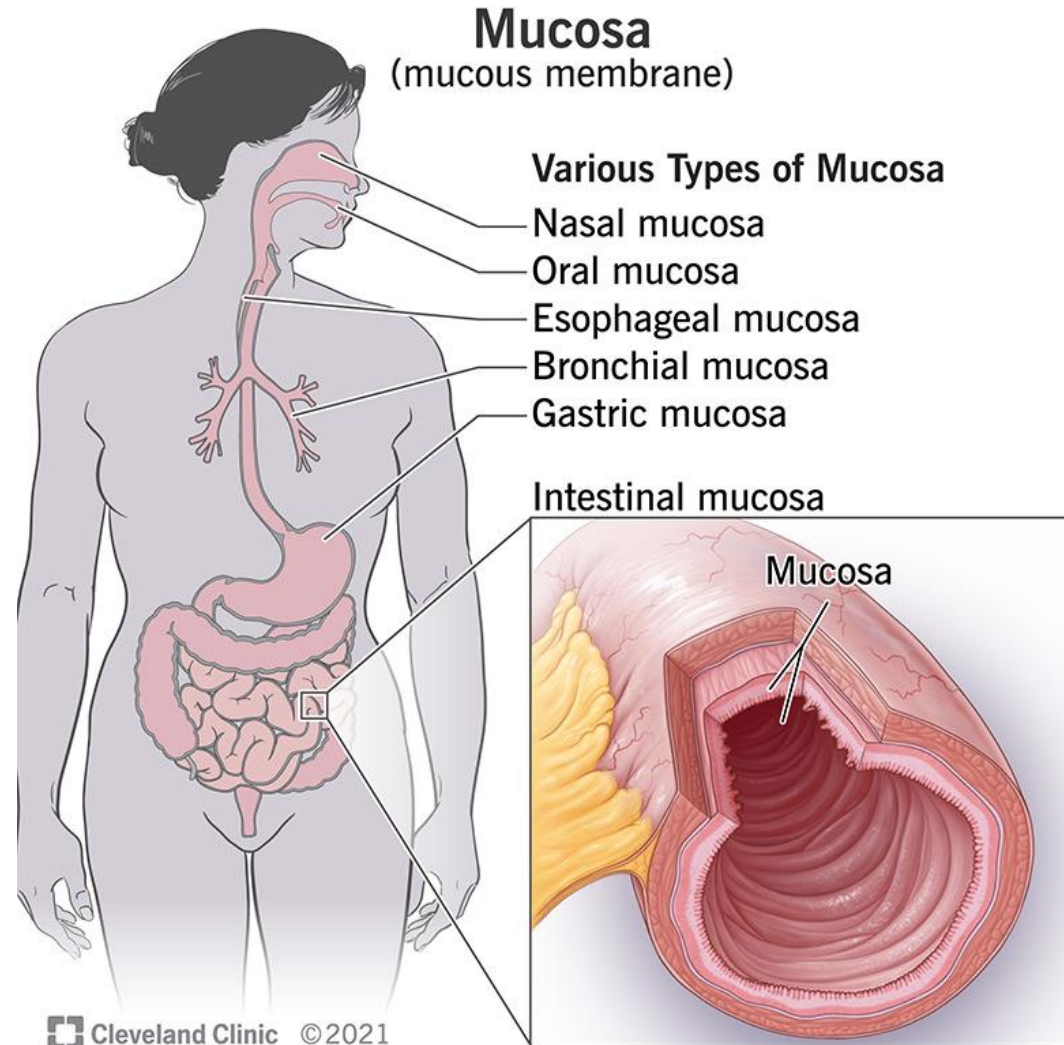




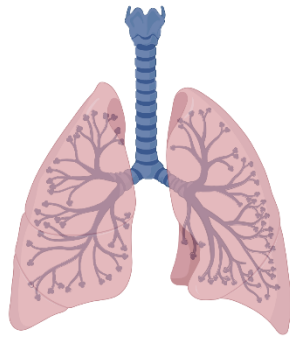
Mechanical stretch in mucosal tissues regulating immune-stromal crosstalk

Do-Hyun Kim, Ph.D
Assistant Professor in Department of Life Science
Hanyang University

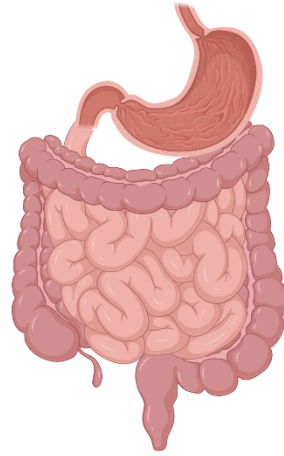
Inner surfaces of the body, mucosal area



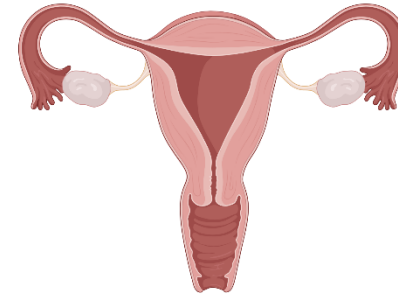
Each mucosal tissue have distinct role



Breathing



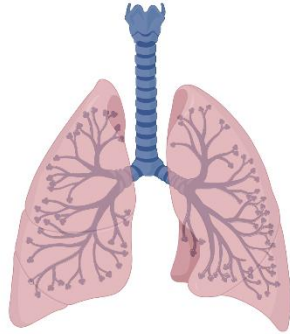
**Digestion
Absorption**



Reproduction

Each mucosal tissue have distinct role

= Each mucosal tissue composed of distinct cell types



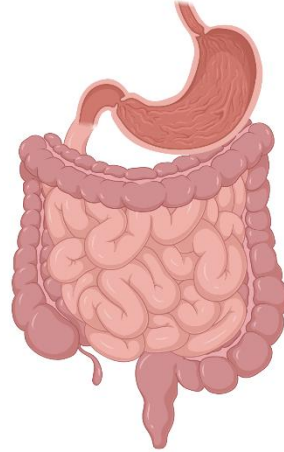
Breathing

AT1
AT2
AEP

.

.

.



**Digestion
Absorption**

Neck cell
Chief cell
Parietal cell
Paneth cell

.

.



Reproduction

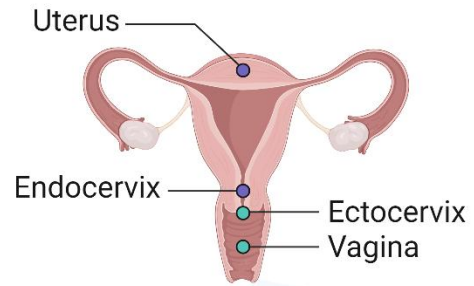
Endometrial cell
Myometrial cell
Smooth muscle cell

.

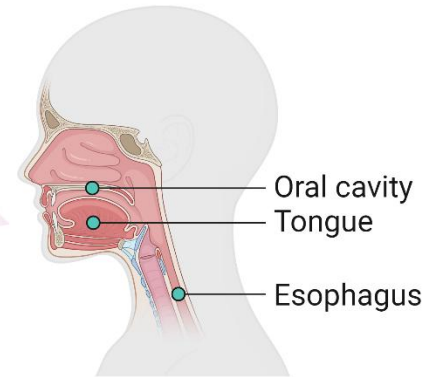
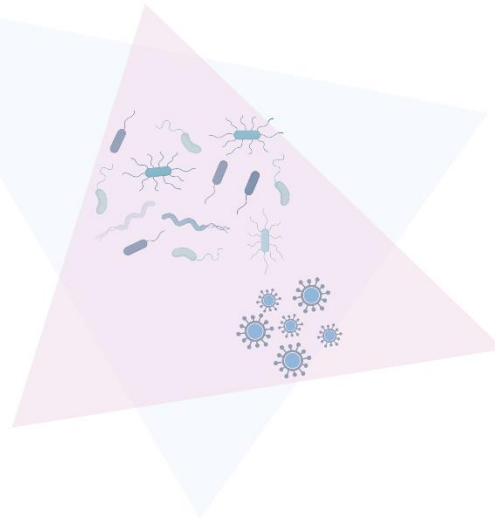
.

.

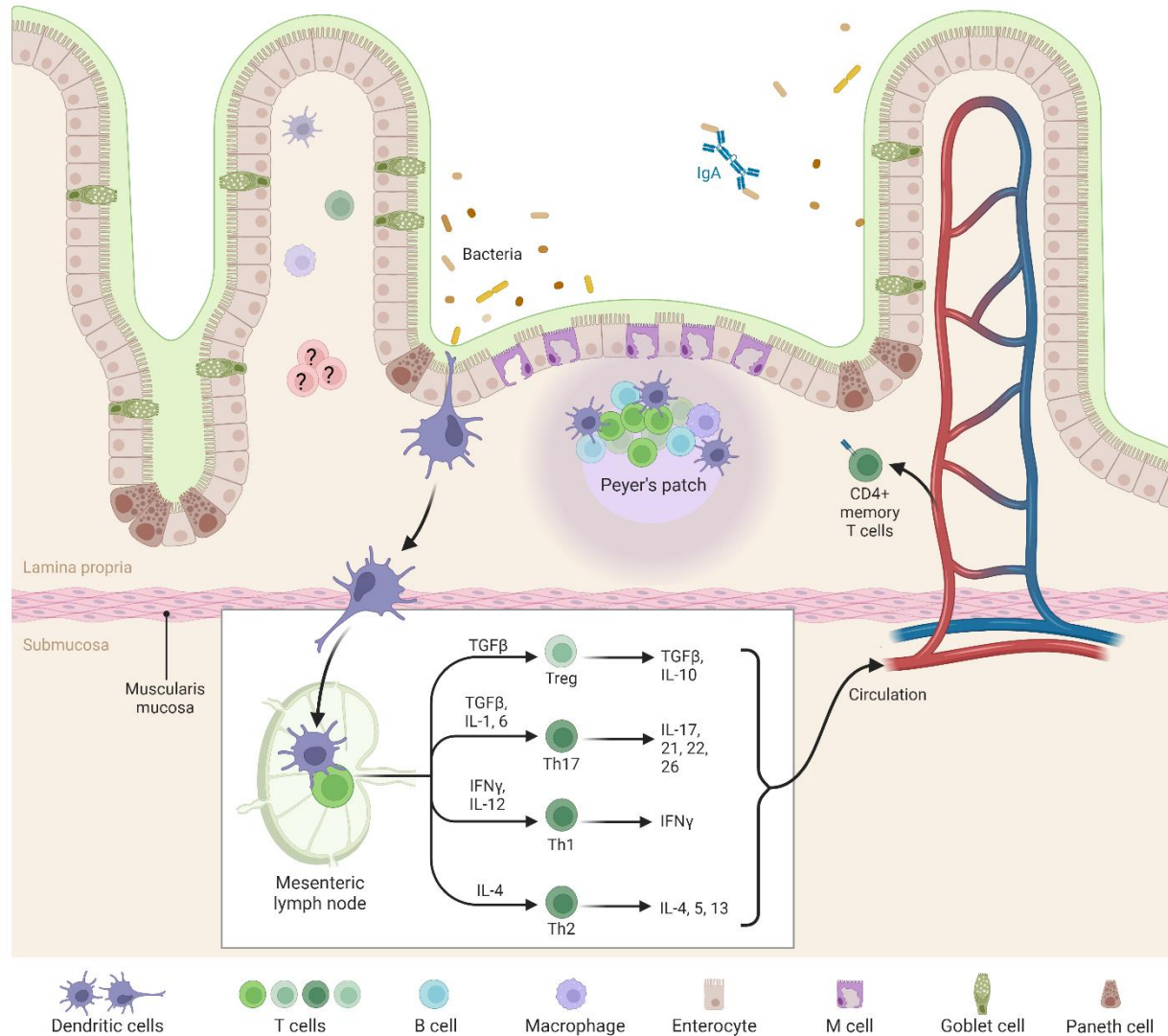
Mucosal tissue is open system



No physical borders so open to exogenous agents such as bacteria / virus / environmental factors

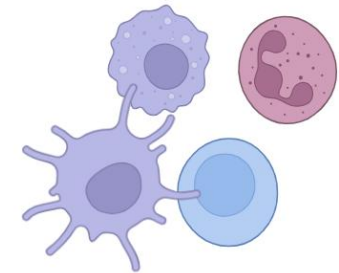


Immune compartment in mucosal tissues to protect host



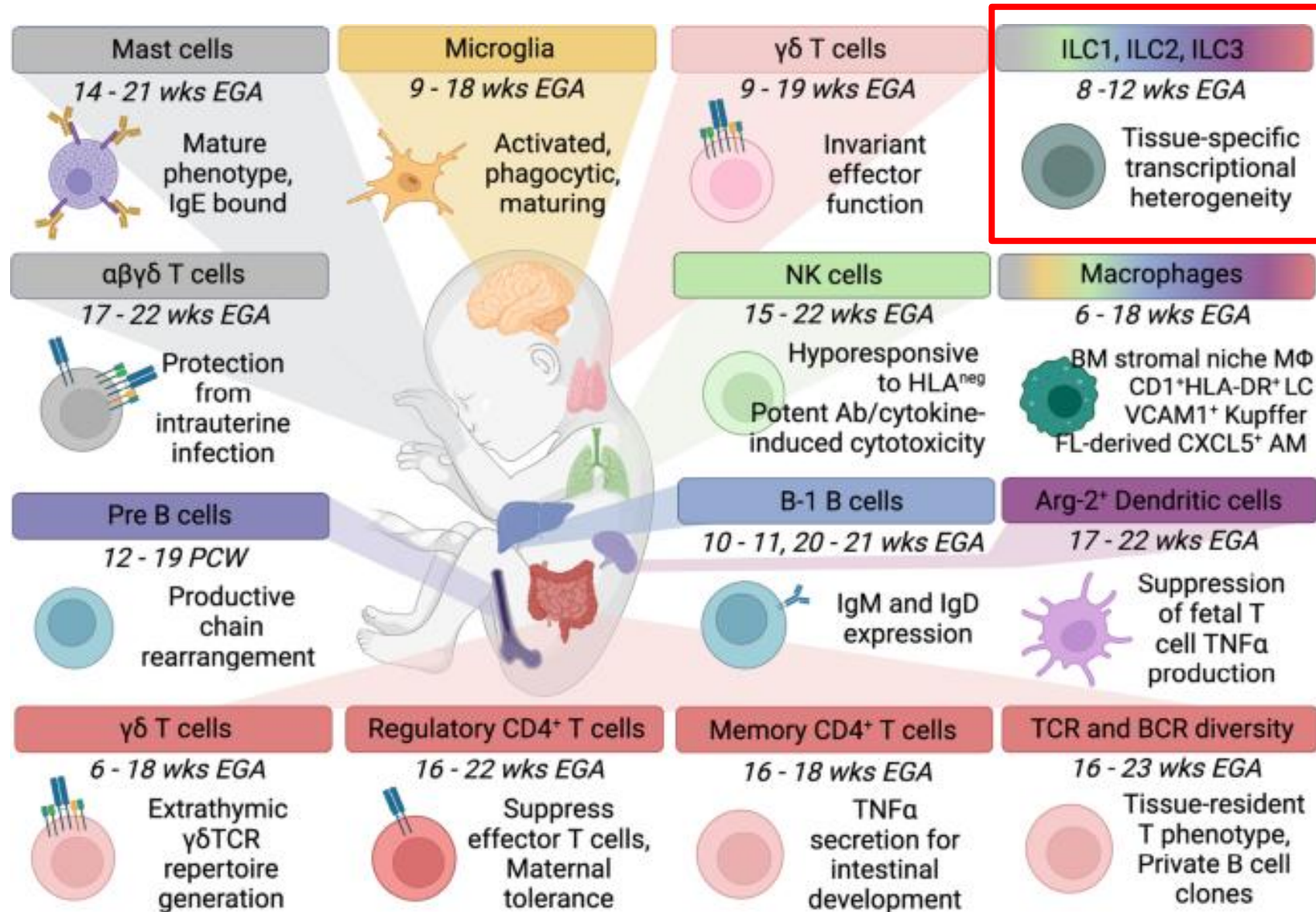
Tissue resident cells

1. Maintain microenvironment
2. Antigen presenting
3. Conditioning cytokine milieu
4. Tissue repair after clearance



Circulating and Tissue Resident cells

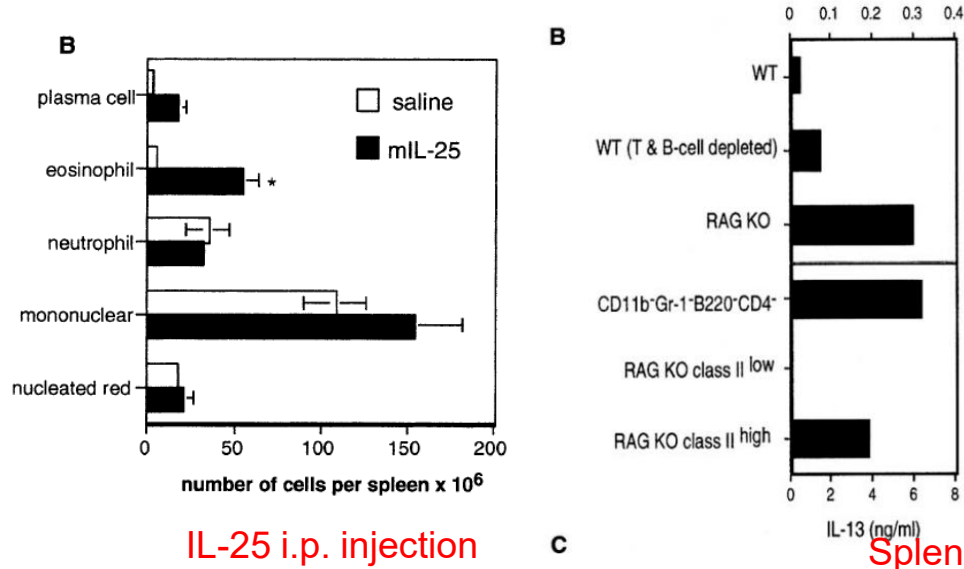
Tissue resident cells



ILCs, unexpected player

- Found accidentally during IL-25 study by

DNAX
RESEARCH INSTITUTE



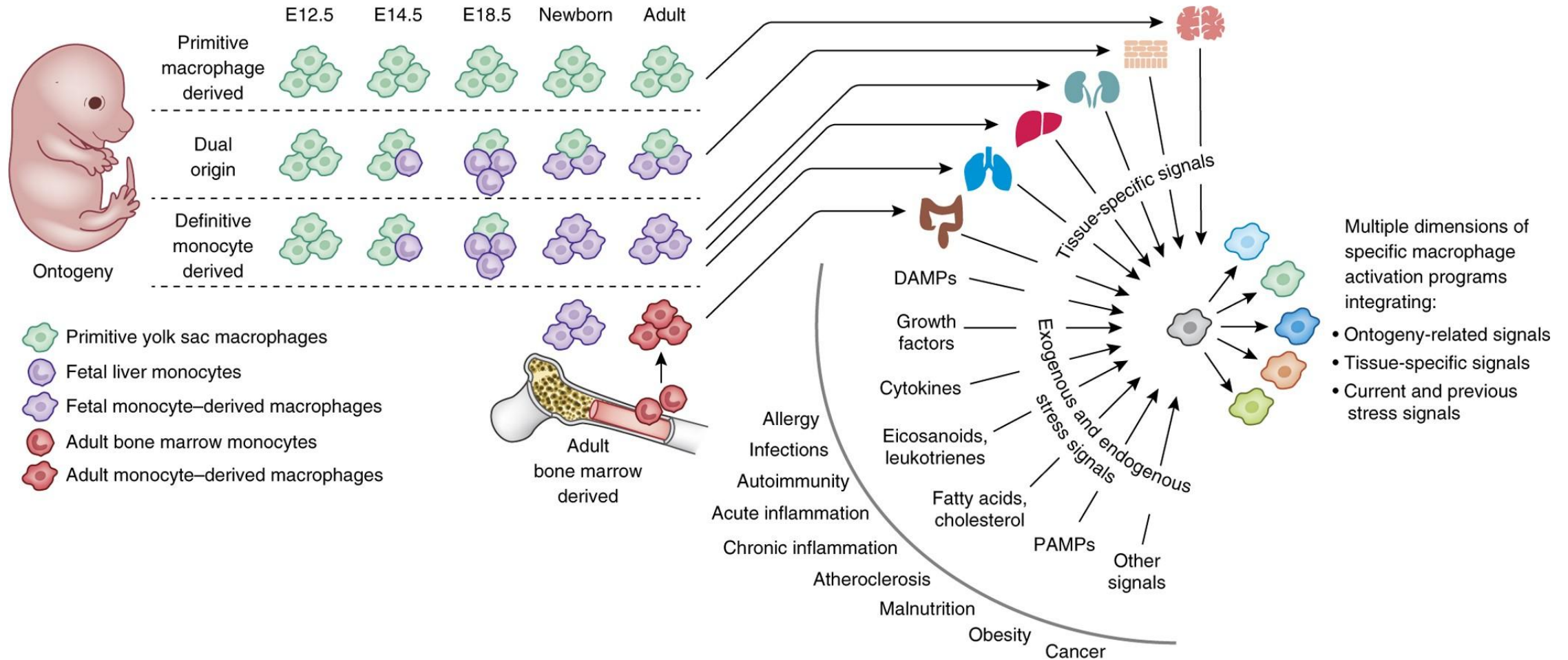
(...) As many different tissues respond to IL-25 treatment by increased IL-5 and IL-13 expression, it is likely that the identified **accessory cell** is widely distributed among different tissues.

2001 Immunity

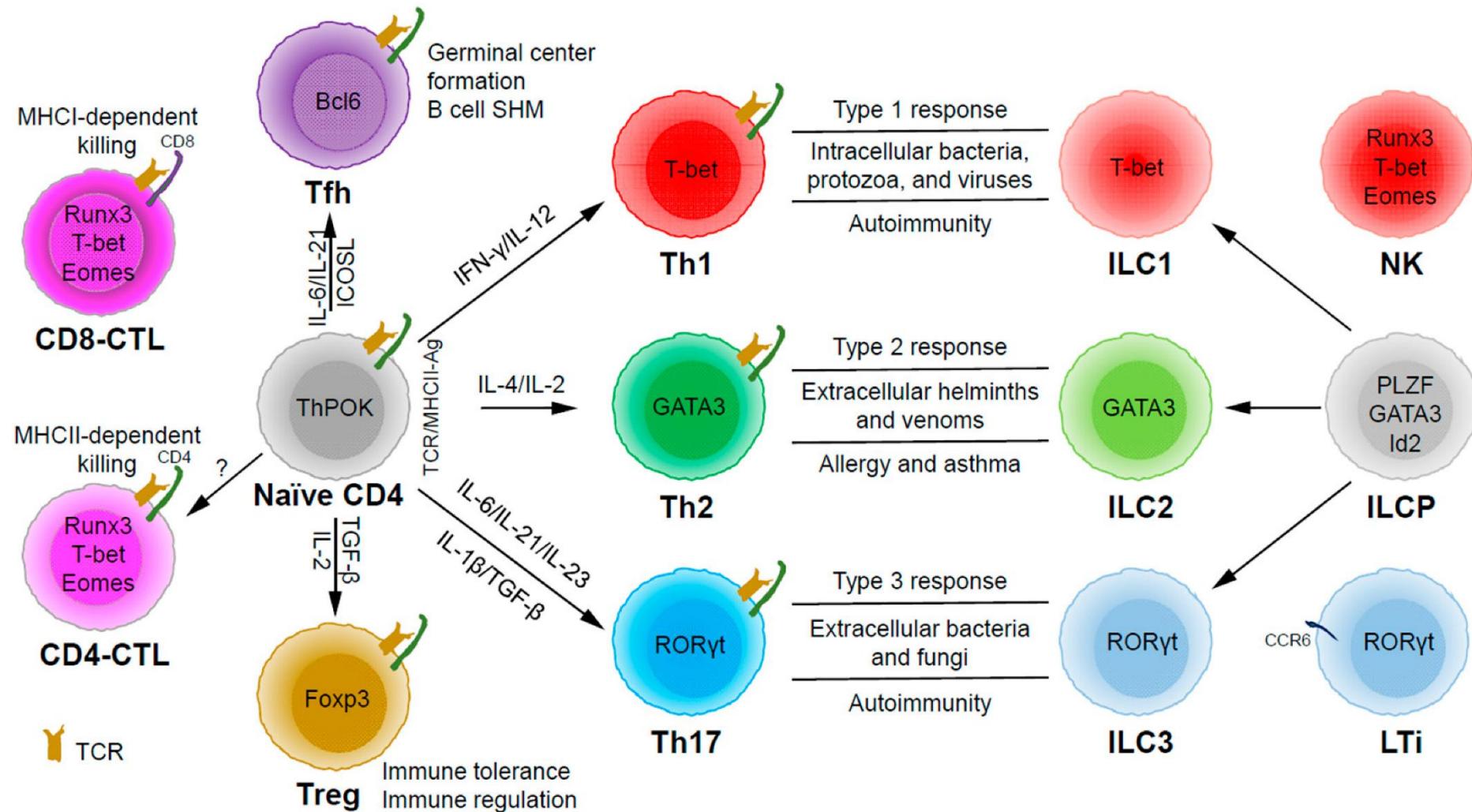
- Nuocyte (2010 Nat, McKenzie)
- Natural helper cell (2010 Nat, Koyasu)
- Innate helper 2 cell (2010 PNAS, Locksley)
- MPP type 2 cell (2010 Nature, Artis)

Uniformed nomenclature
as **Innate Lymphoid** Cell
(2013 NRI)

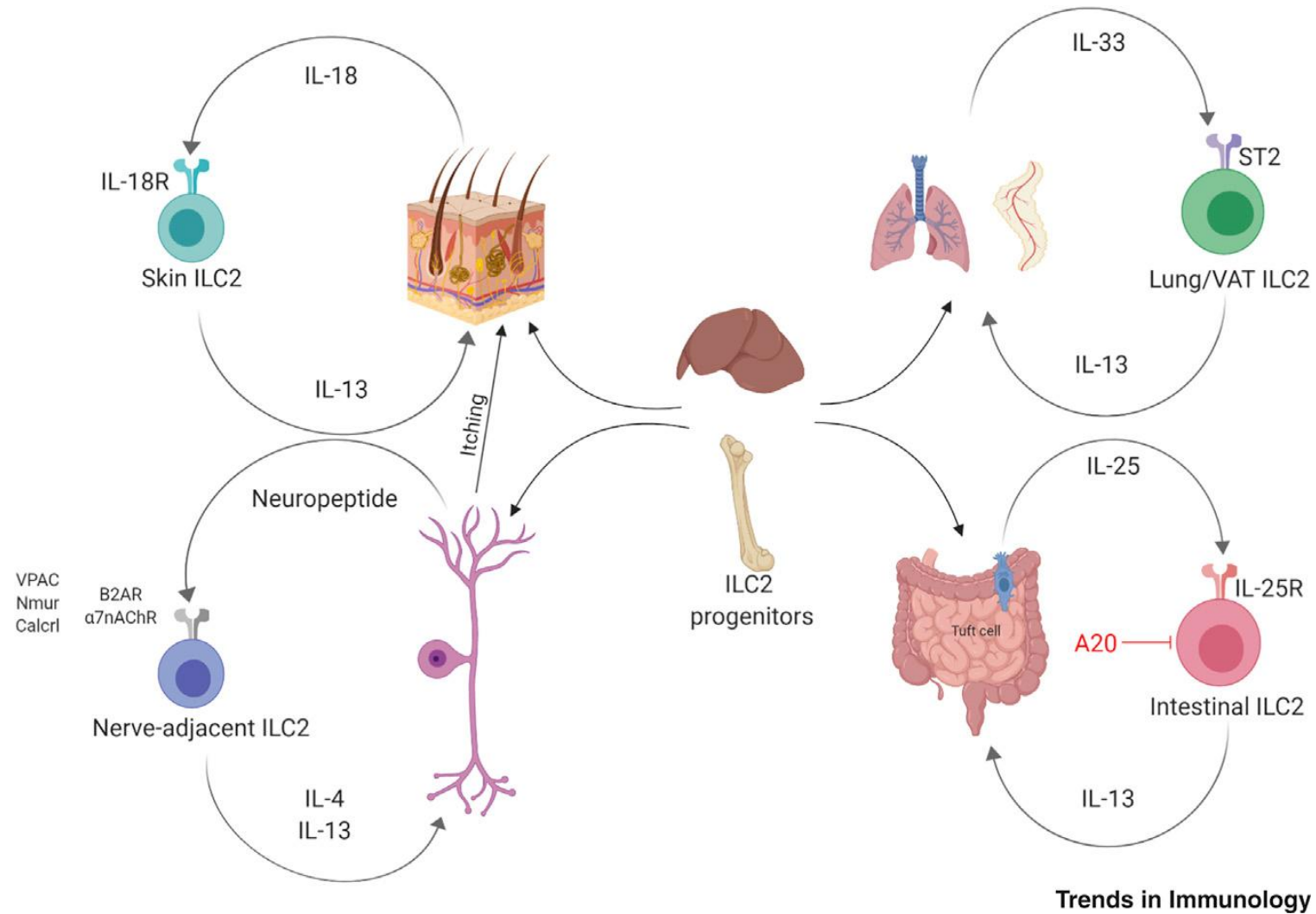
ILC showed similar distribution pathway with TRM



ILC showed similar character with helper T cell

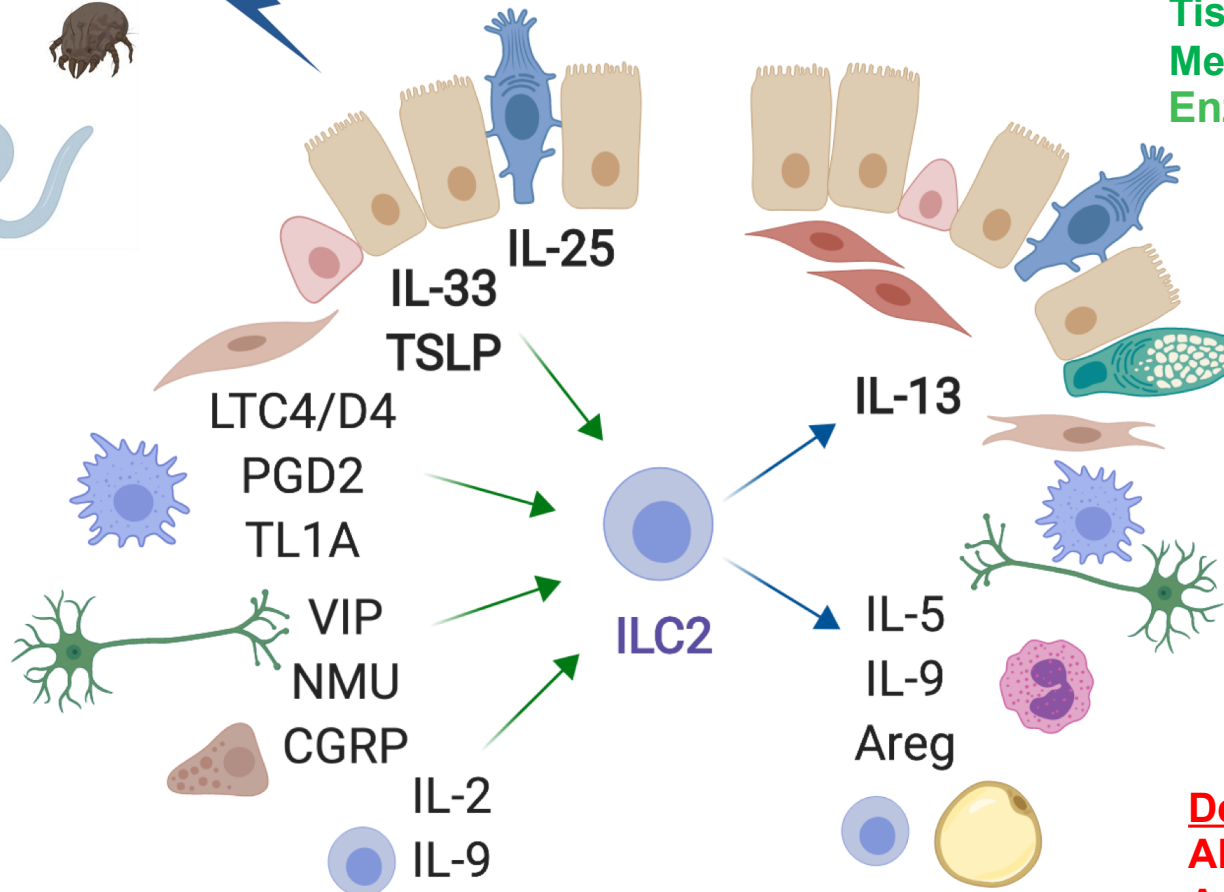


ILC2s matured by tissue niche



Role of ILC2s in mucosal tissues

Tissue perturbation,
chemosensation



Restorative

Wound healing

Tissue remodeling

Metabolic homeostasis

Enzyme induction

2020 Bando et al

2023 Balmas et al

2023 Kim et al

2024 Jung et al

Detrimental

Allergy

Asthma

Atopic dermatitis

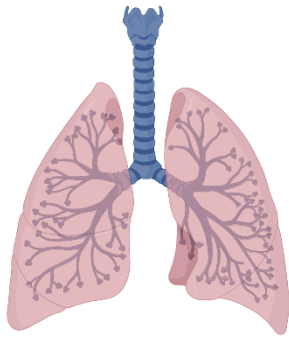
2012 Kim et al

2017 Wallrapp et al

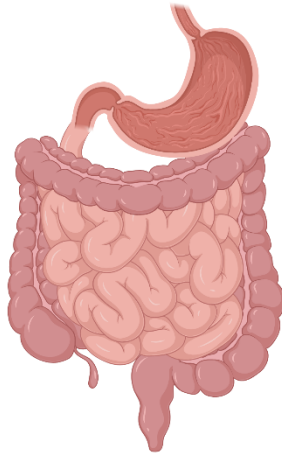
2018 Van Dyken et al

2020 Kim et al

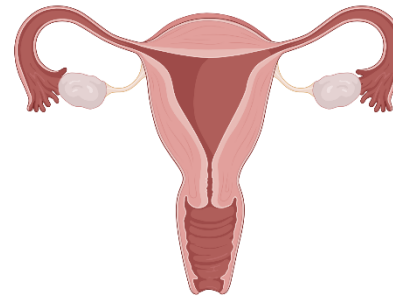
ILC2s are almost everywhere, but we don't know it's role in some place



Breathing



Digestion
Absorption



Reproduction

Skin
Muscle
Brain
Liver
Fat
Salivary glands

.
. .
. .

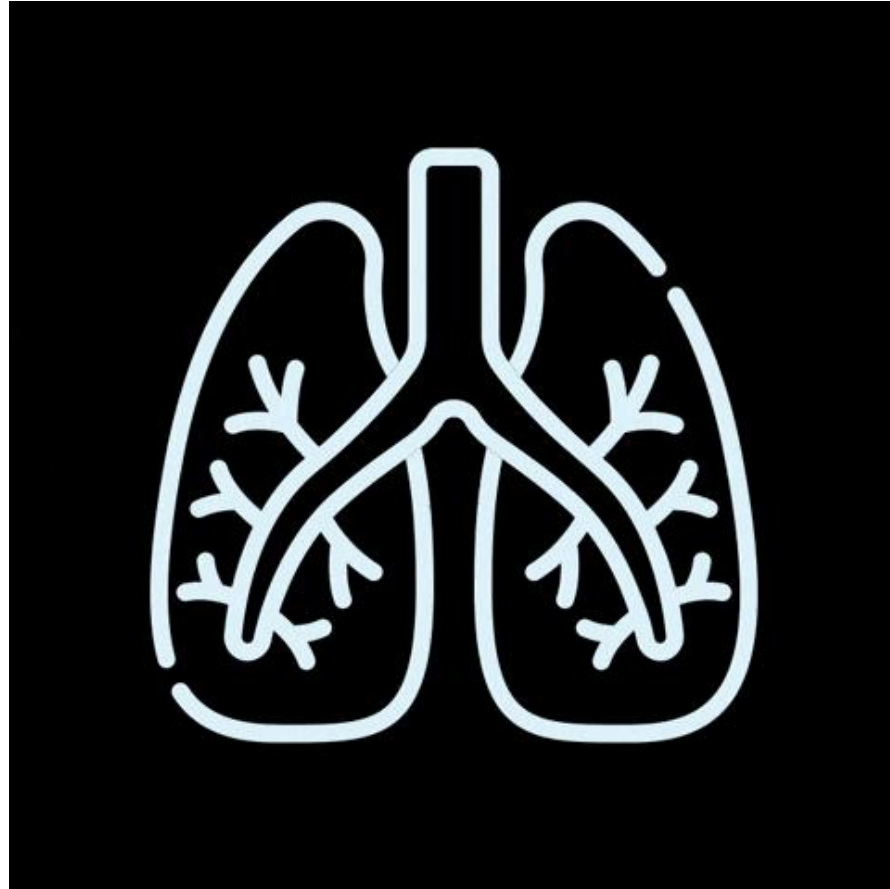
Role of ILC2s in the stomach

Bacteria-Induced Group 2 Innate Lymphoid Cells in the Stomach Provide Immune Protection through Induction of IgA, *2020 Immunity*

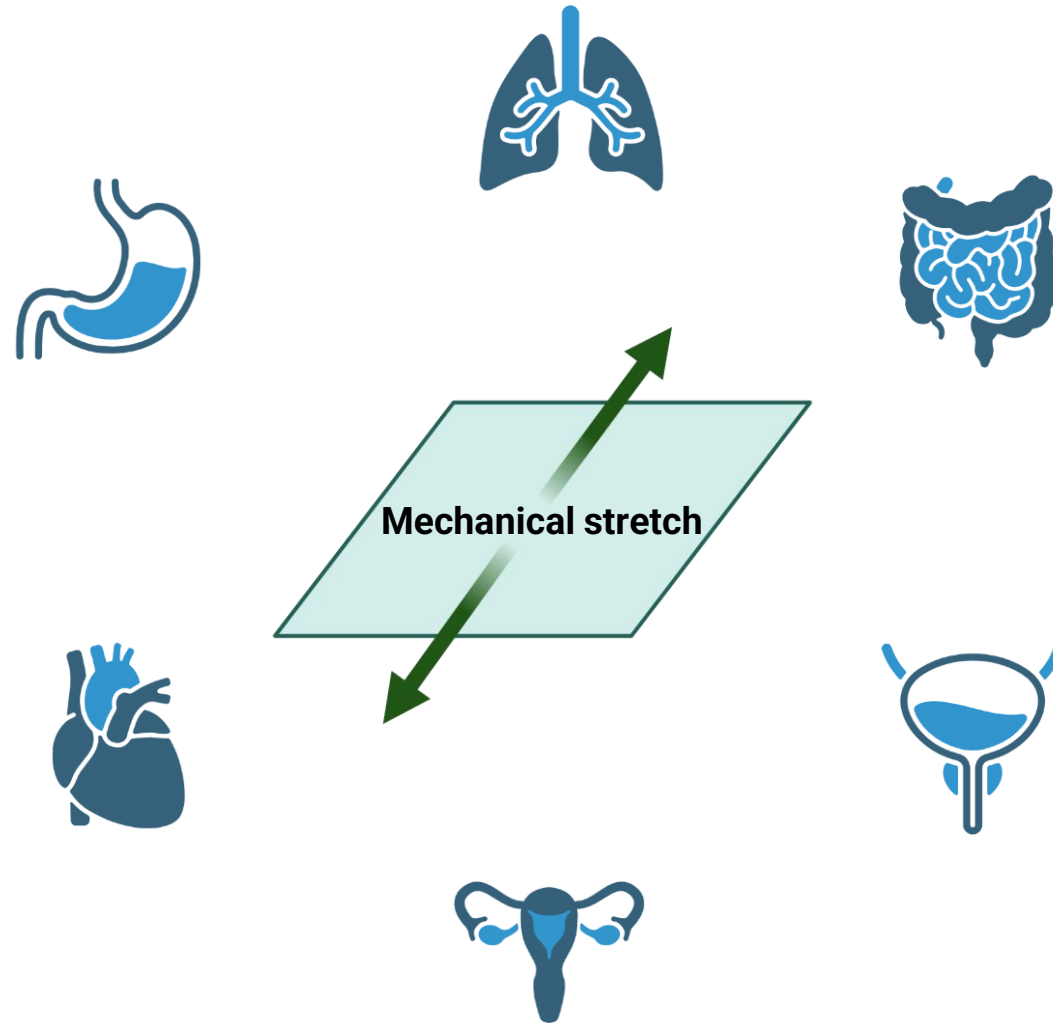
Group 2 Innate Lymphoid Cells Coordinate Damage Response in the Stomach, *2020 gastroenterology*

A tuft cell - ILC2 signaling circuit provides therapeutic targets to inhibit gastric metaplasia and tumor development, *2023 Nat comm*

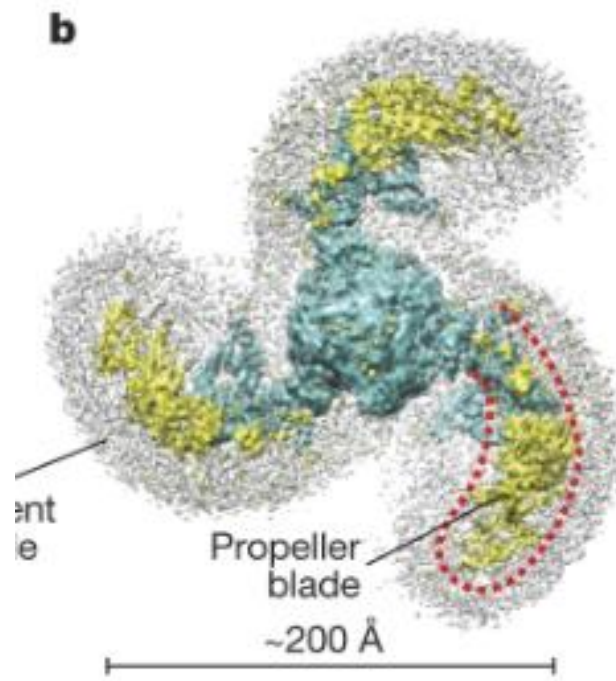
Mechanical stretch in living an organism



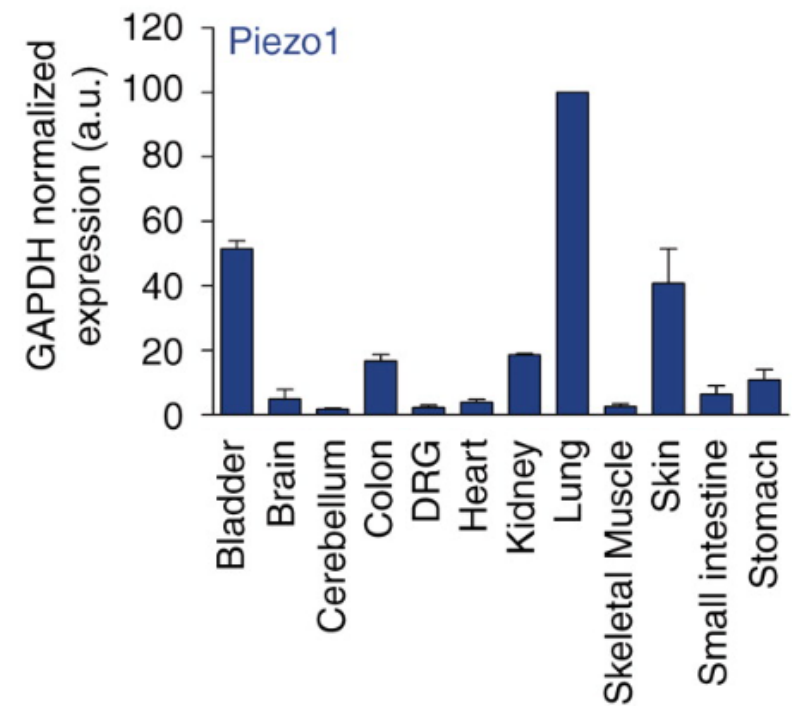
Mechanical stretch in peripheral tissues



Piezo1, mechanosensory receptor

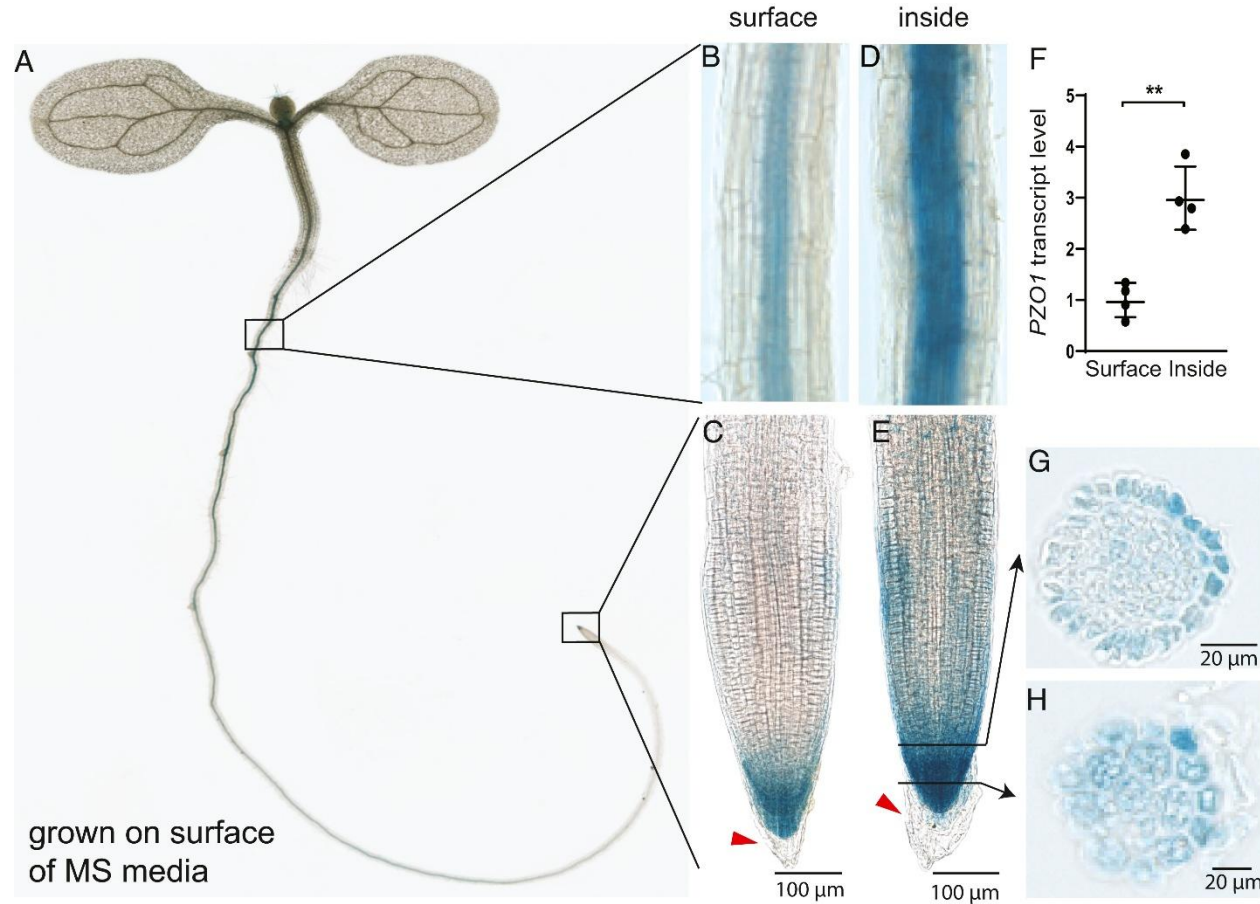


2017 *Nature*

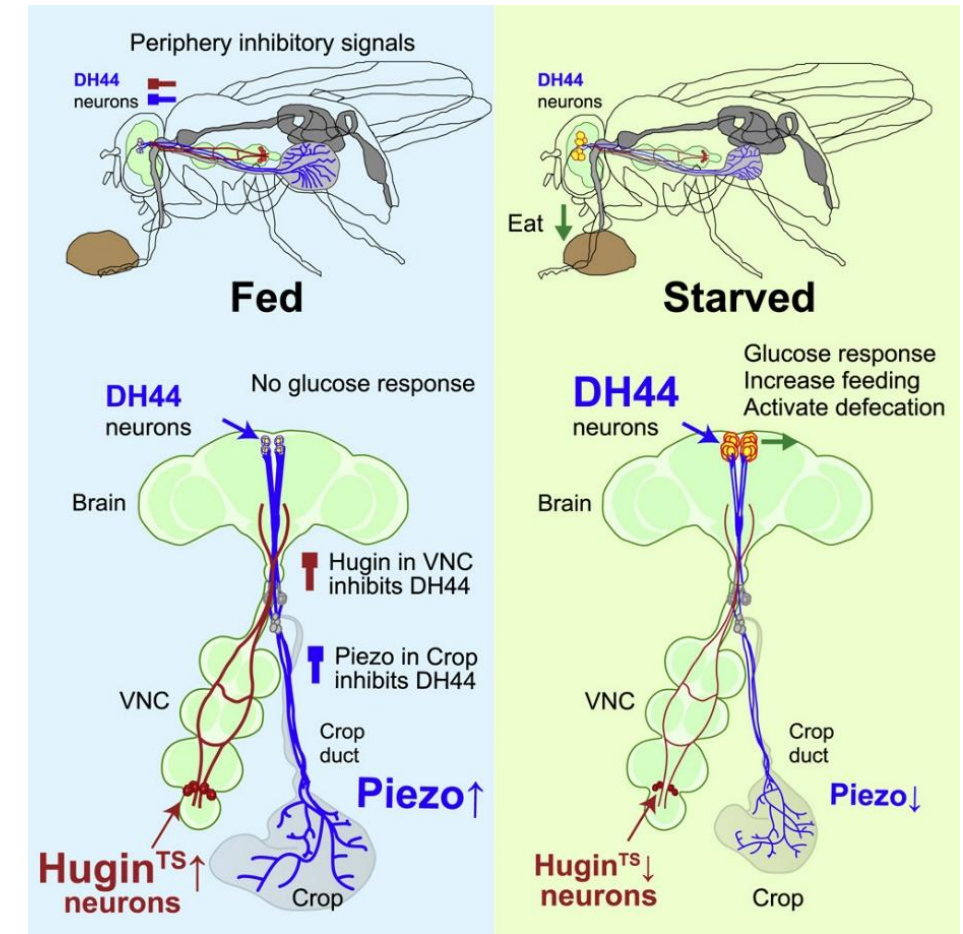


2010 *Science*

Piezo1 is evolutionarily conserved mechanosensory receptor

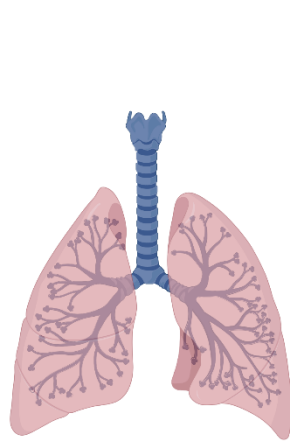


2021 PNAS

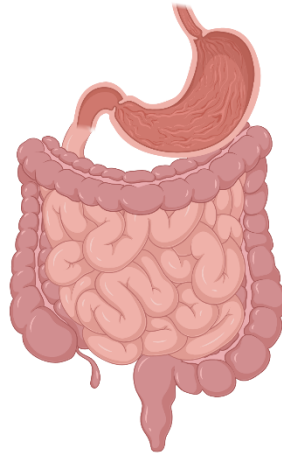


2021 Neuron

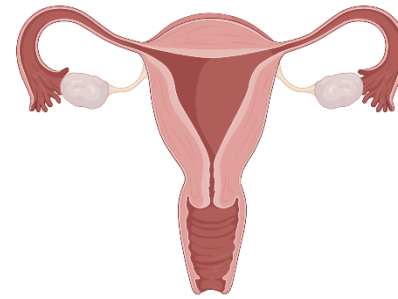
Mechanical stretch is common stimulus in mucosal tissues



Breathing



Digestion



Pregnancy
/ Delivery

Q. What is the role of ILC2s in mucosal tissue, especially with mechanical stretch?

Experimental scheme

1. Mechanical stretch



Reason to choose chitin

1. Abundant in the nature
2. Not well digested in rodent gut
3. Host express enzymes

2. Reporter mouse model

YRS mouse (WT)

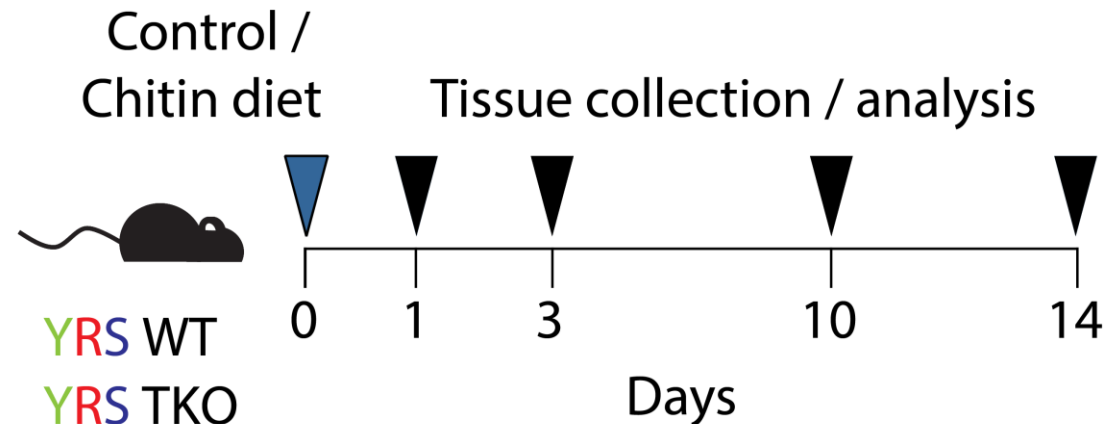
Y;Arginase-YFP: ILC2 surface marker

R;IL-5-RFP: Cytokine spontaneously expressed by ILC2

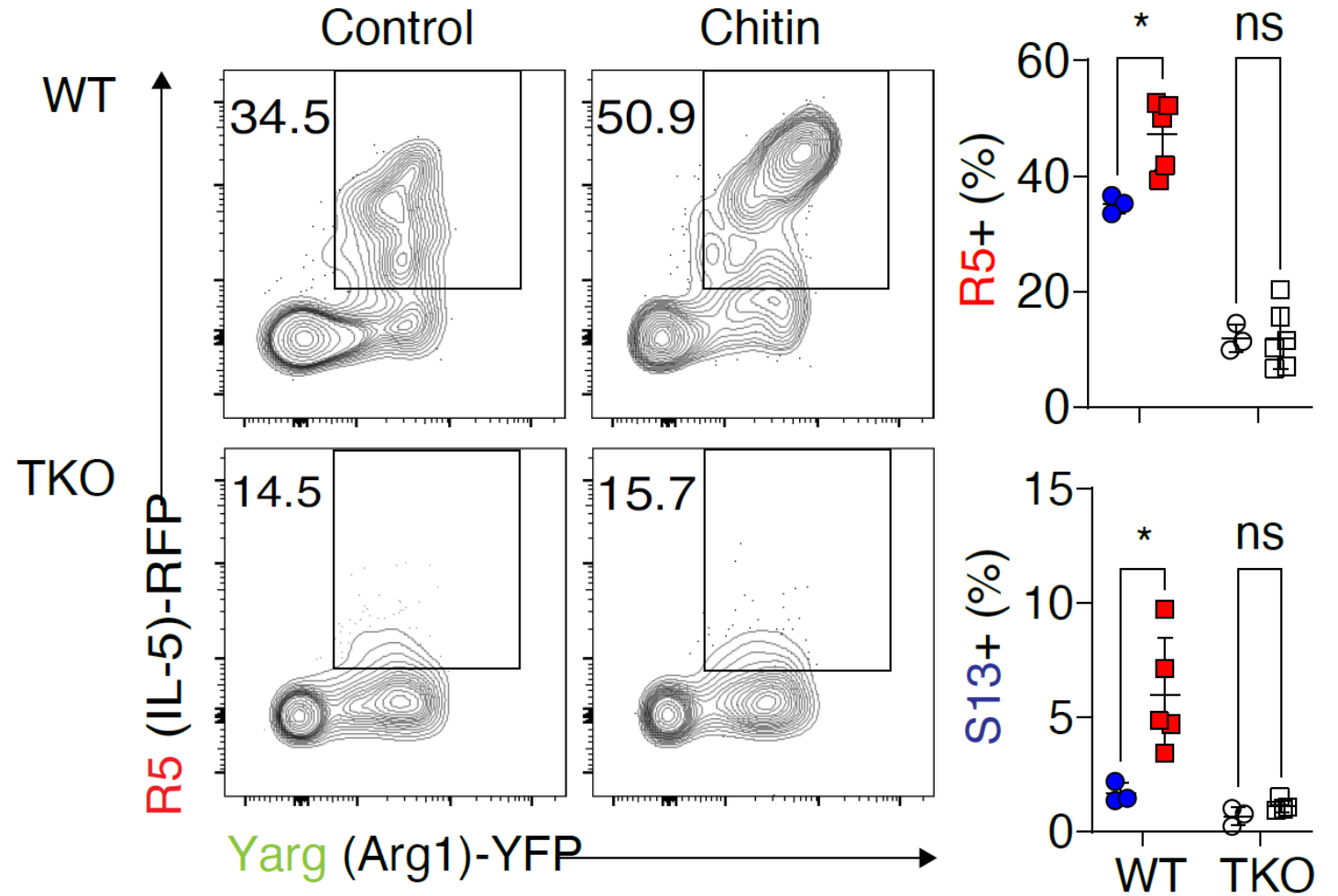
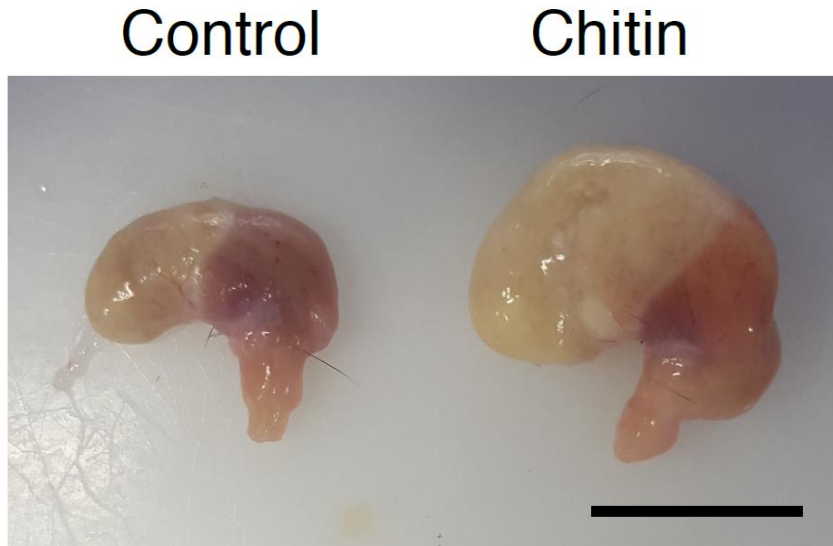
S;IL-13-human CD4: Cytokine expressed by activated ILC2

with IL-25 KO / ST2 KO / TSLPR KO (Triple KO; TKO)

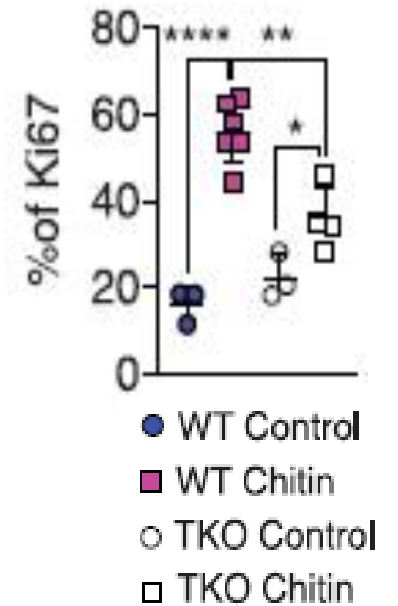
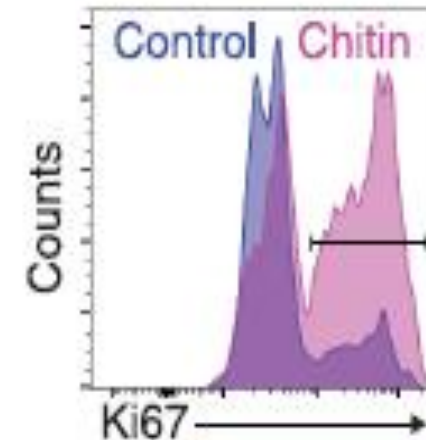
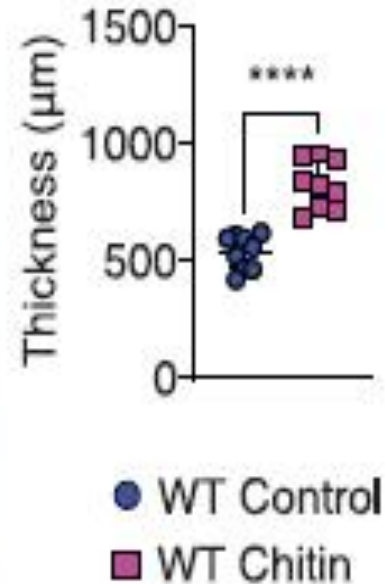
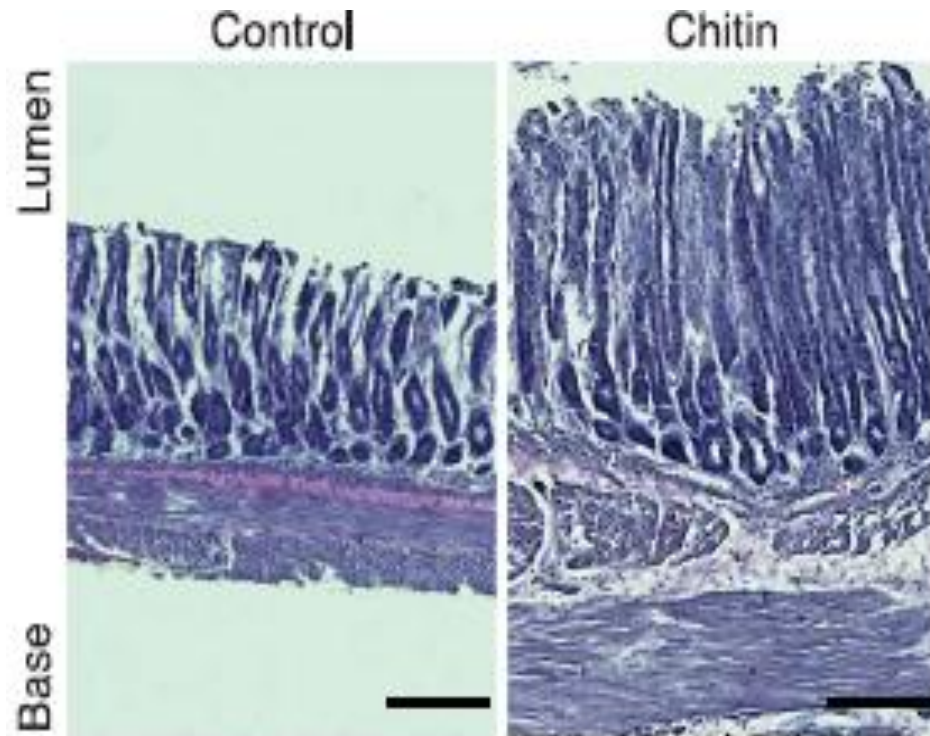
3. *Ad libitum* feeding



Dietary chitin mediated gastric stretch induces type 2 immune activation



Increased gastric type 2 activation induces gastric hyperplasia



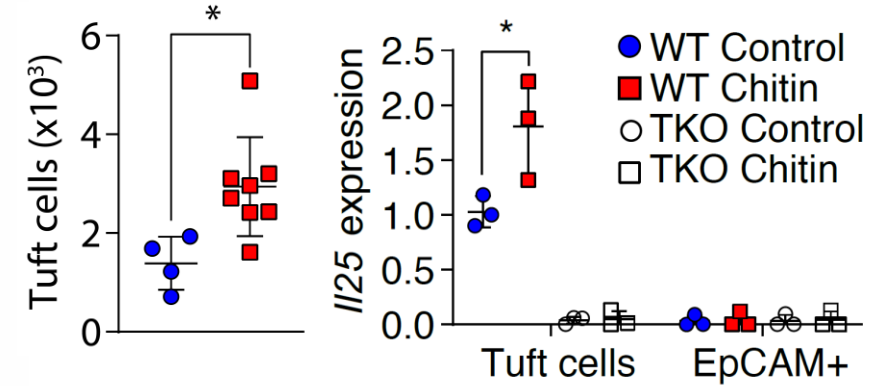
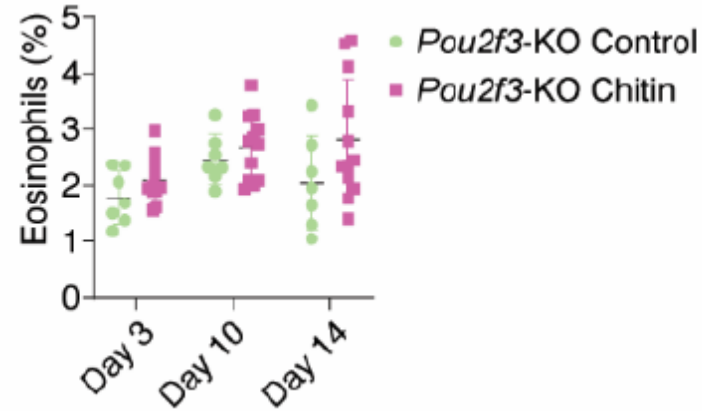
Which factor activate gastric ILC2s by mechanical stretch?

1. Which alarmin?

IL-33?: X

IL-25?: O

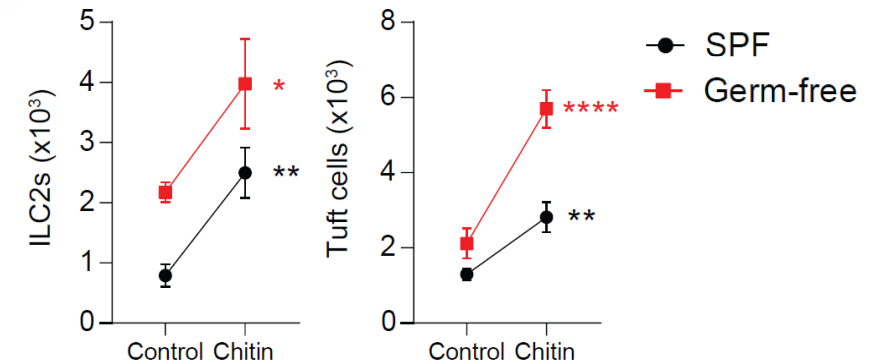
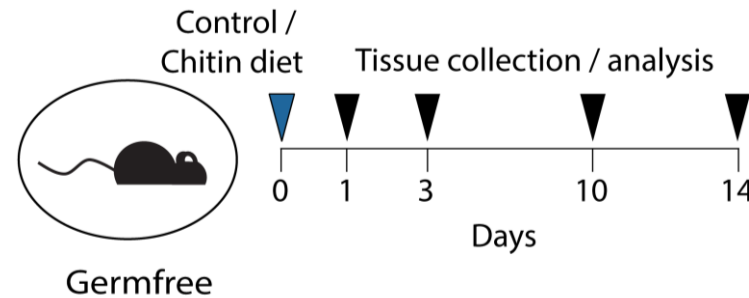
TSLP?: X



2. Microbiome?

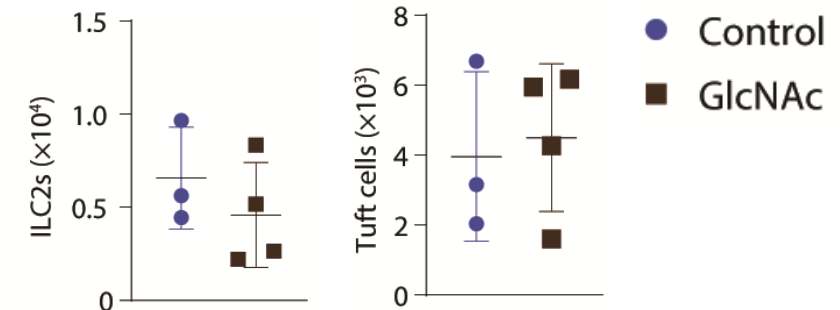
Abx?: intact

GF? : intact

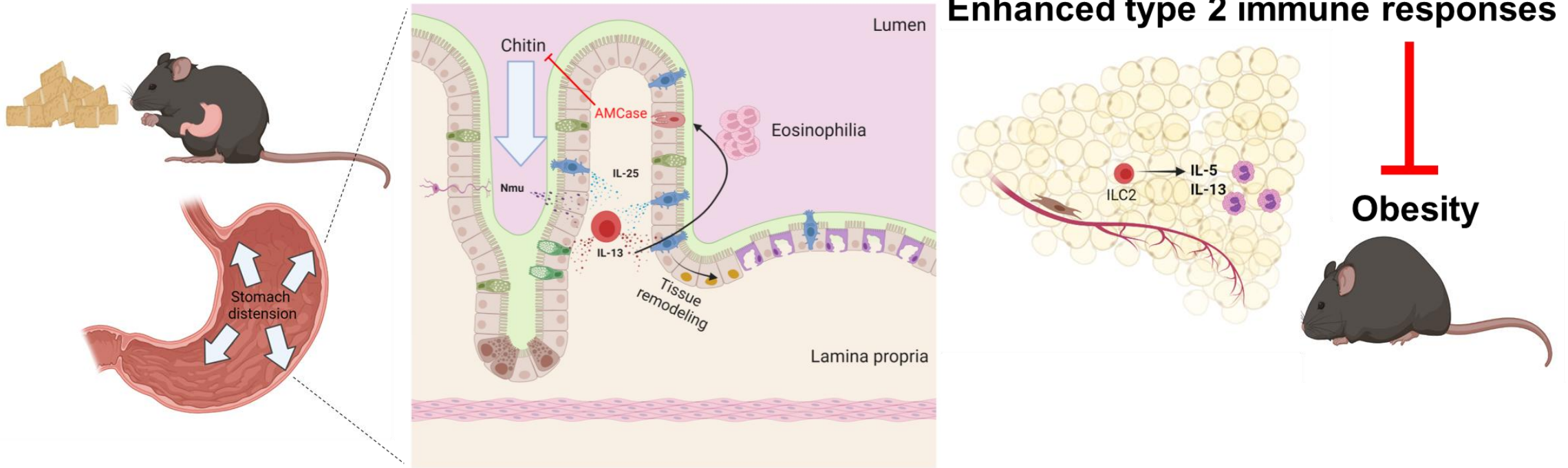


3. Metabolite?

GlcNac: intact



Stomach stretch activate gastric ILC2 circuits

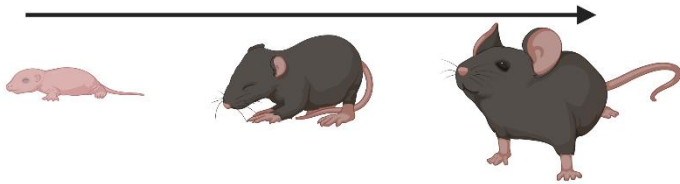


Key point. Chitin diet could induce gastric ILC2 activation with stretch dependent manner

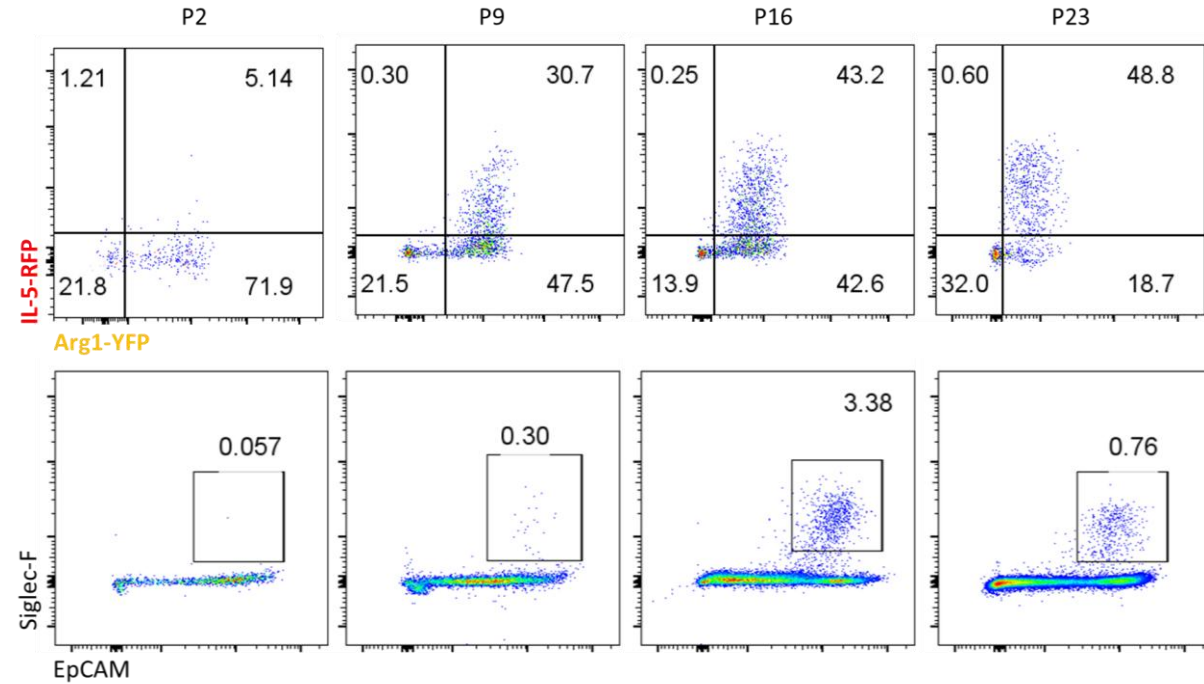
Further Q. Is mechanical stretch involved in gastric ILC2 maturation?

Tuft cell required for gastric ILC2 activation

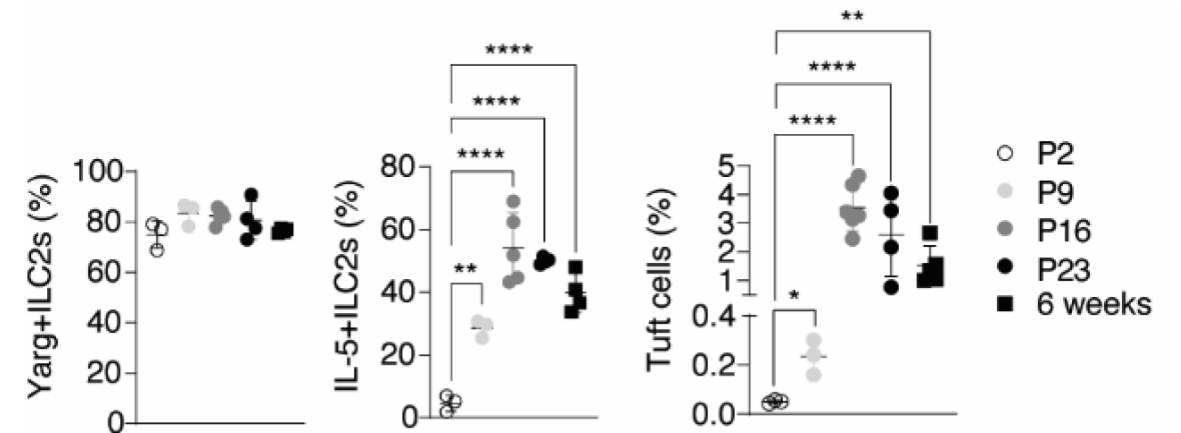
Time dependent analysis



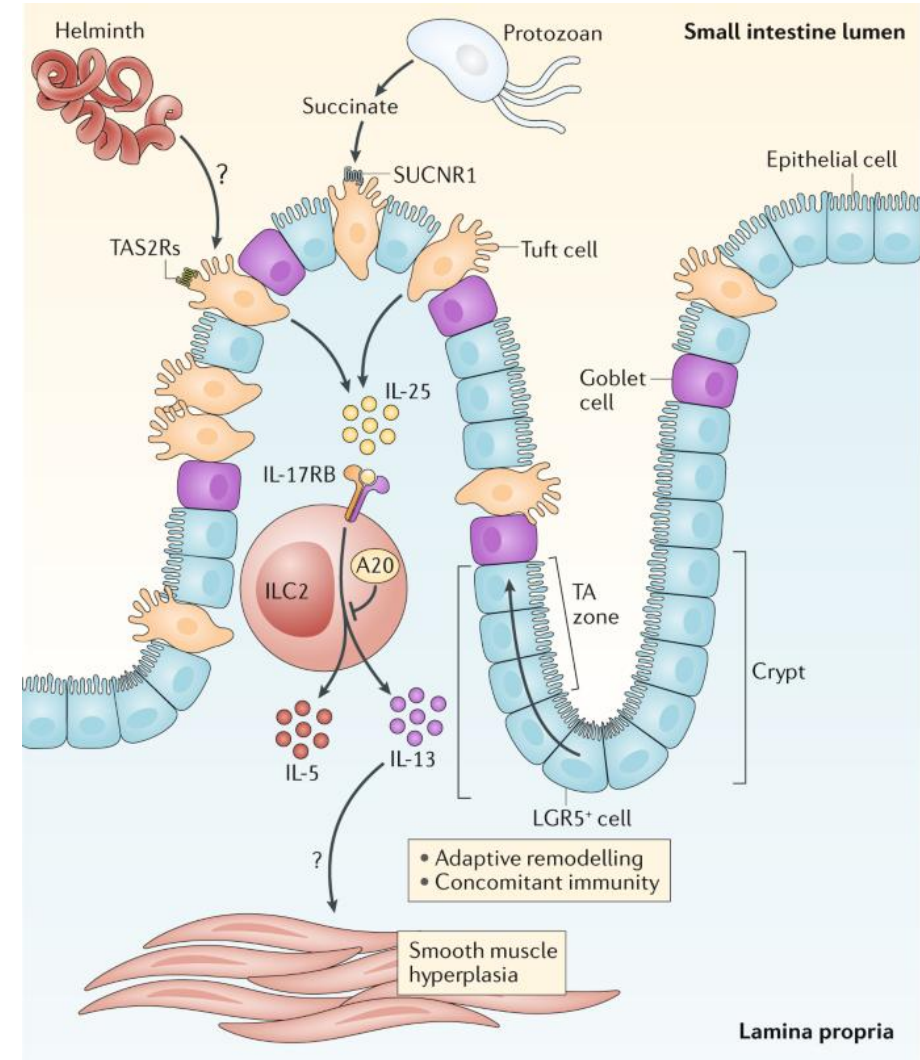
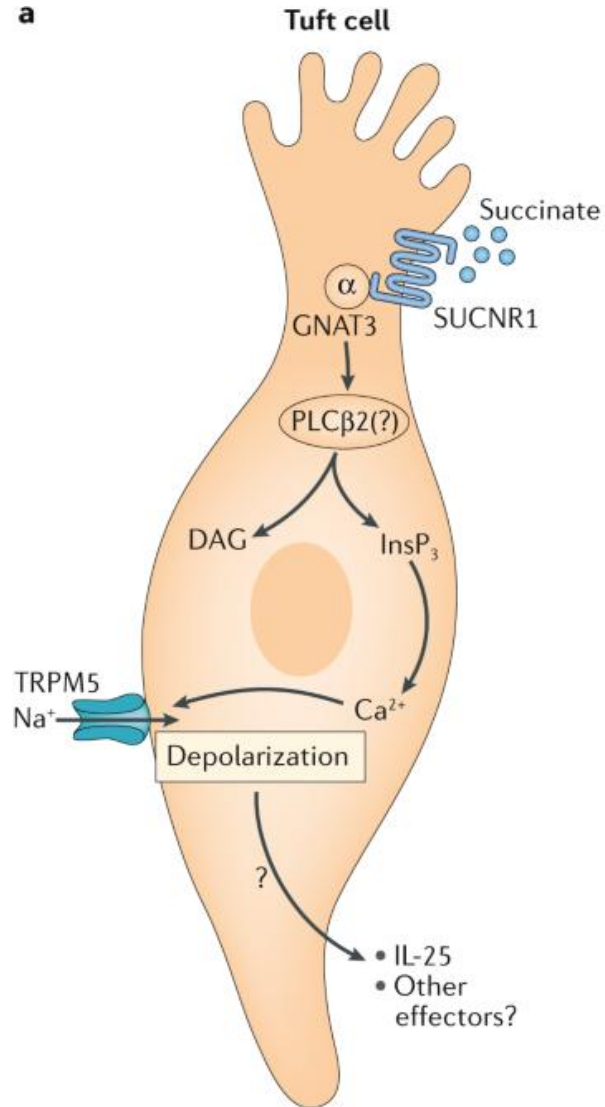
ILC2s



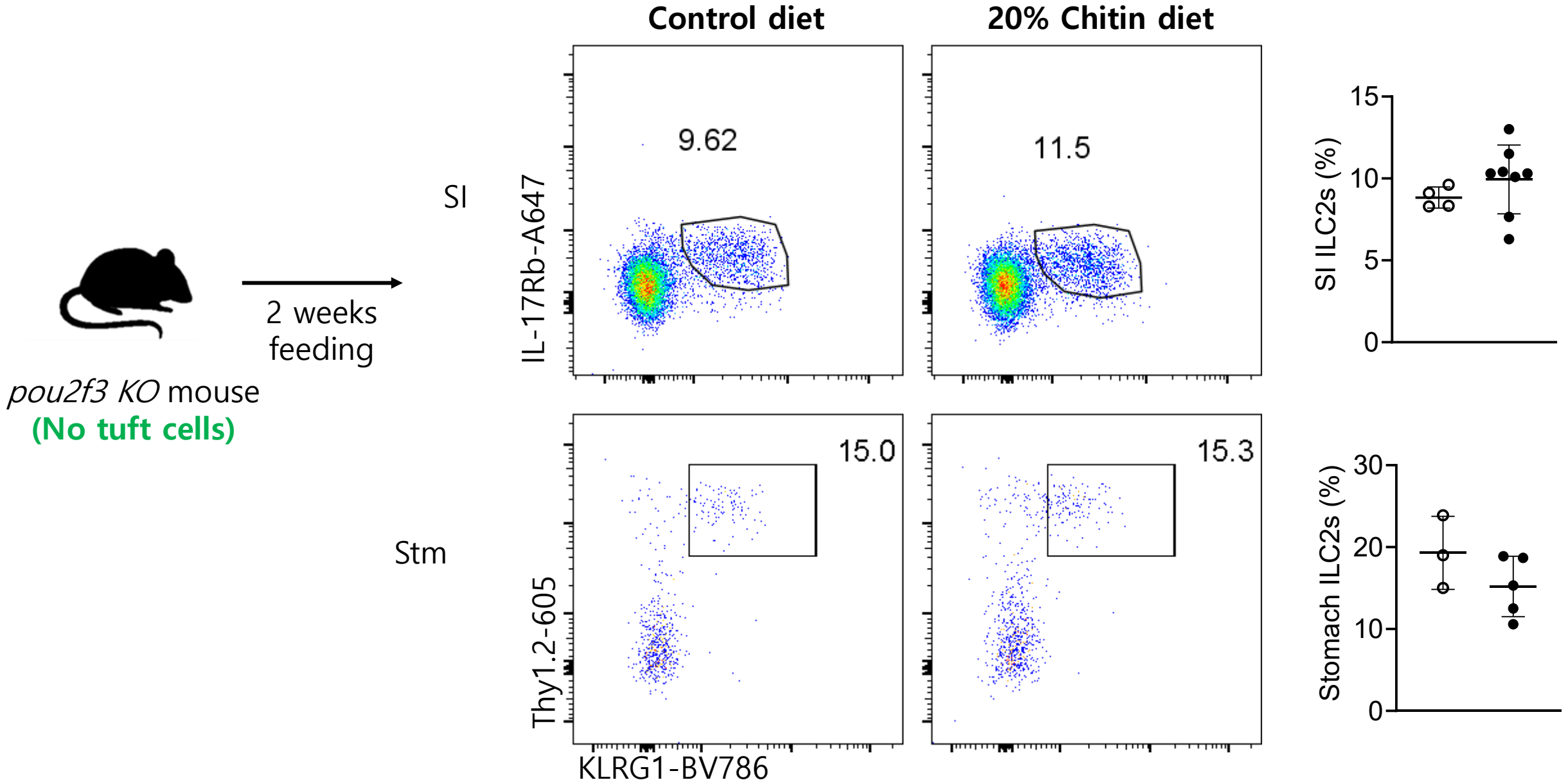
Tuft cells



Role of Tuft cell in intestinal tissues



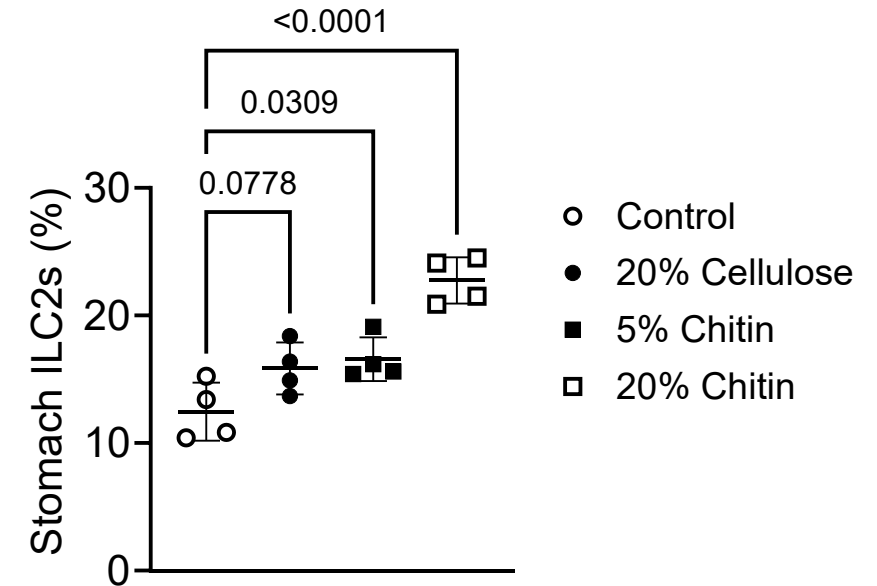
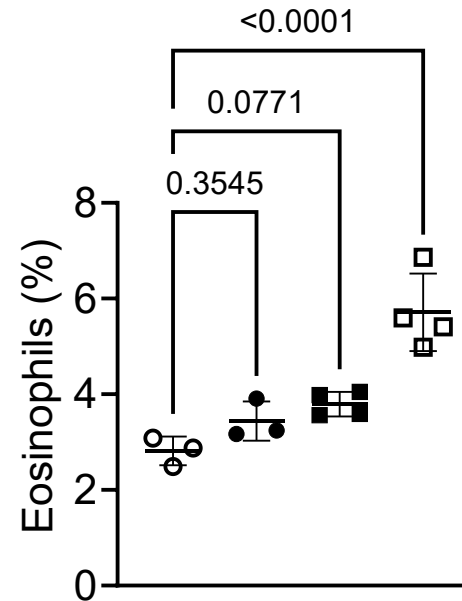
Tuft cell required for stretch-mediated ILC2 activation



Insoluble fiber induce gastric type 2 activation with size dependent manner

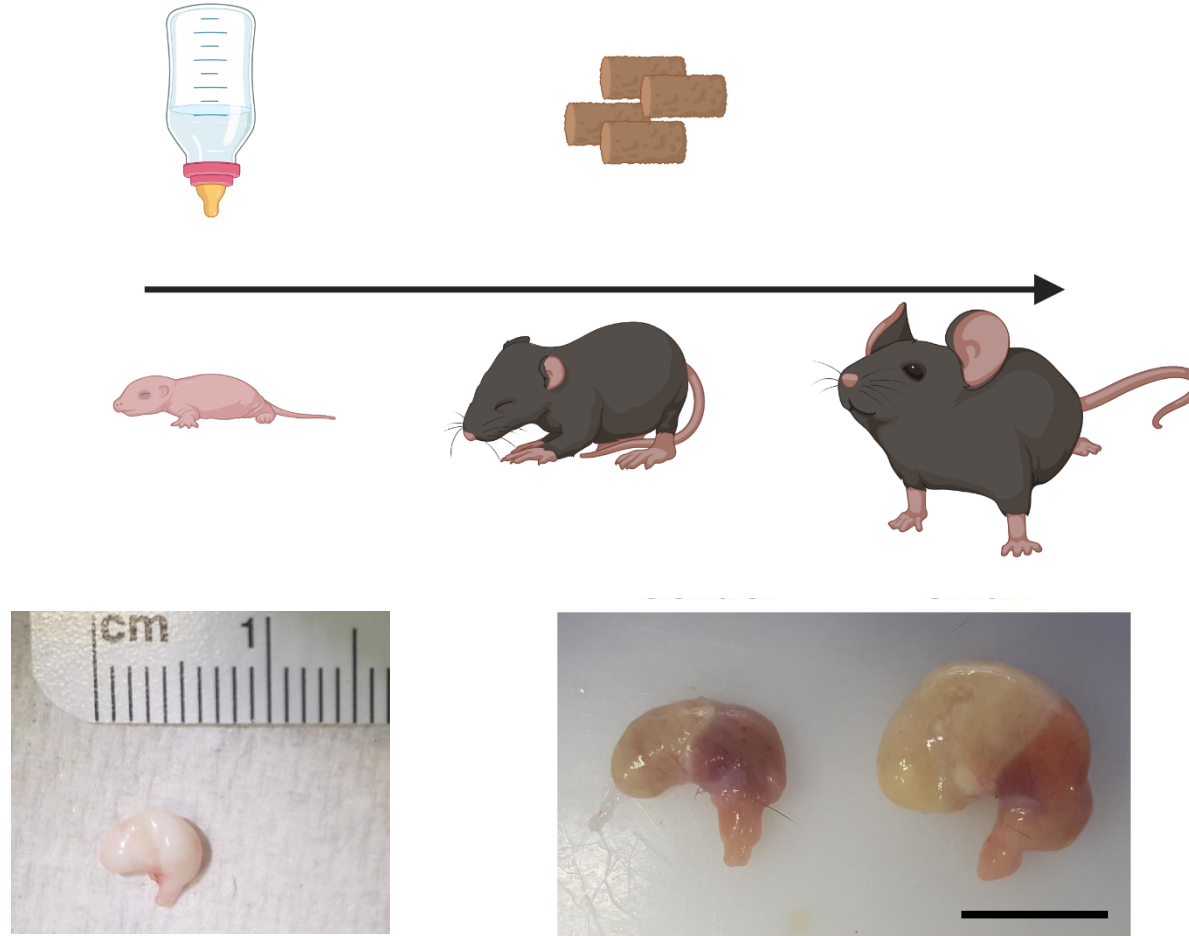


2 weeks of special diet
Particle size: Chitin > Cellulose

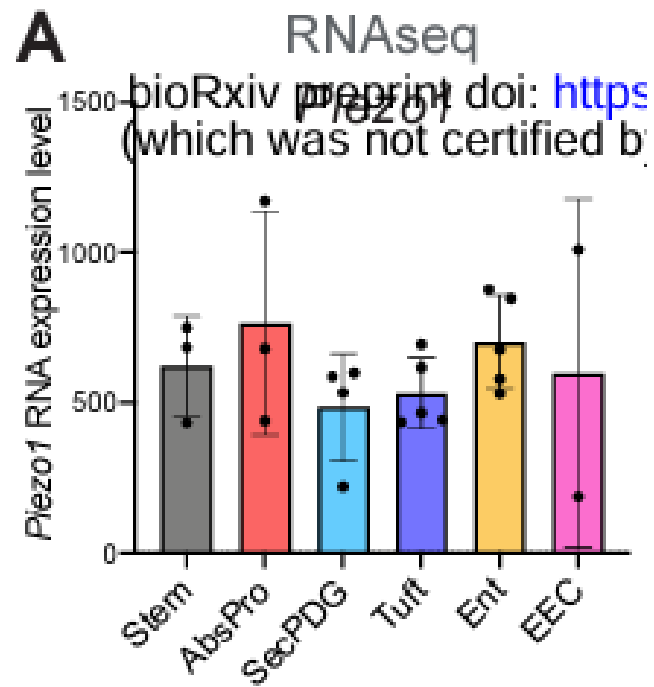


(unpublished data)

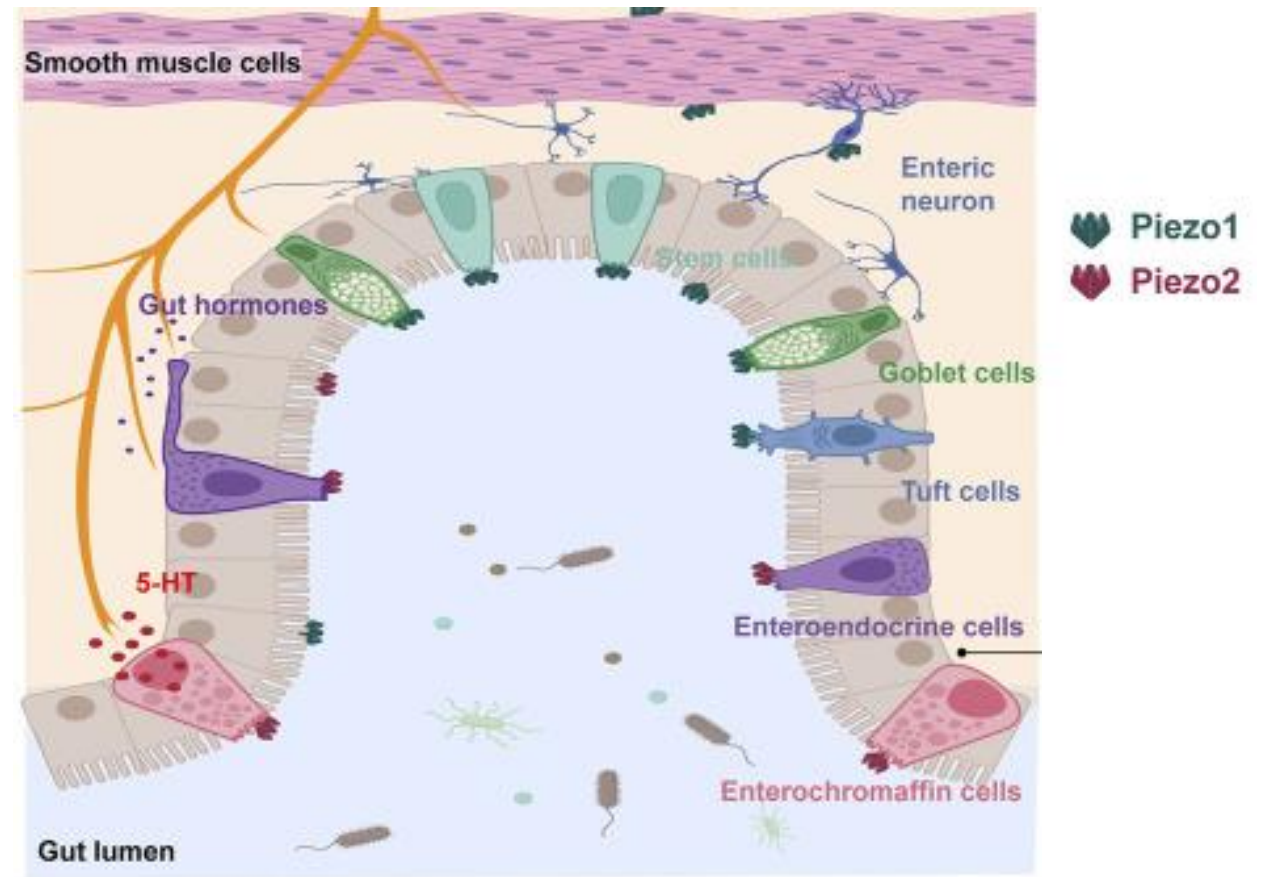
How gastric tuft – ILC2 circuits activated in nature



Tuft cell may sense mechanical stretch in stomach

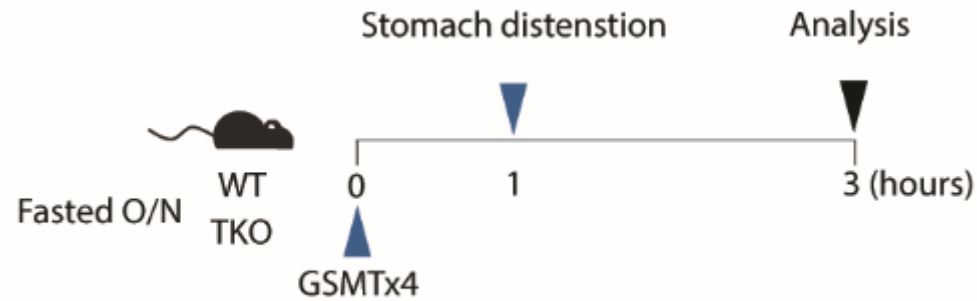
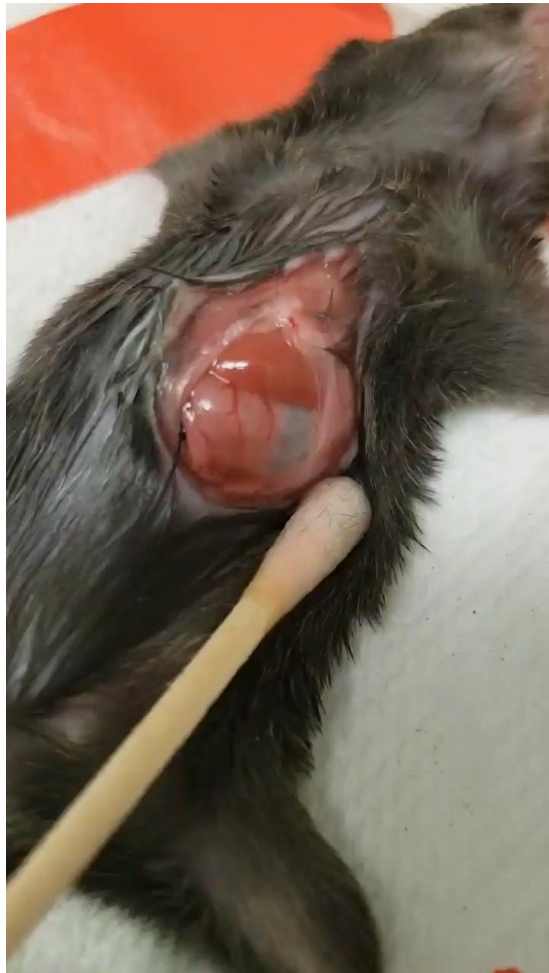


2024 Biorxiv



Modified, 2024 front Physiol

Even pure mechanical stretch is enough to induce tuft cell activation

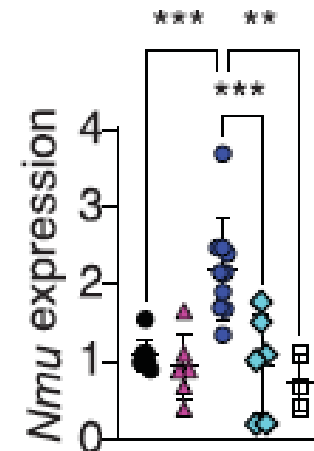
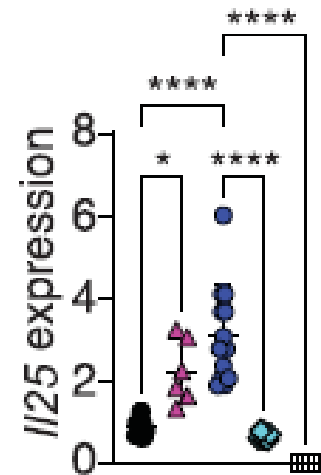


GSMTx4 : Spider Venom Peptide.
Inhibits Cationic-Permeable
Mechanosensitive Channel

Control



Inflated



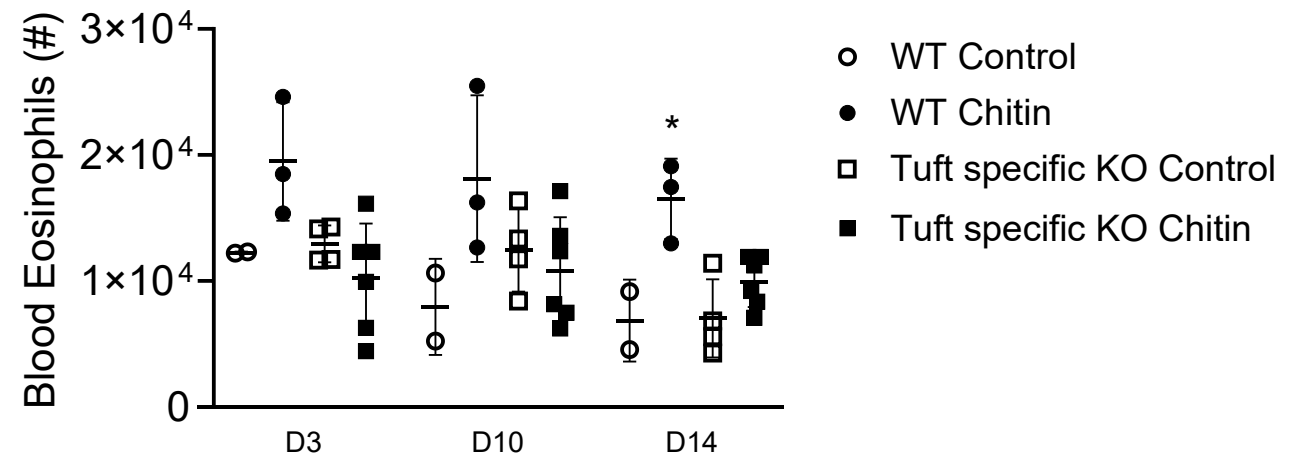
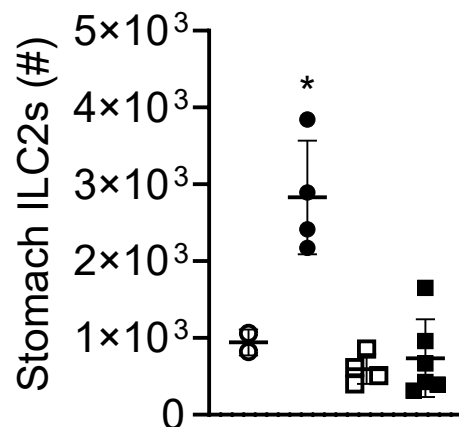
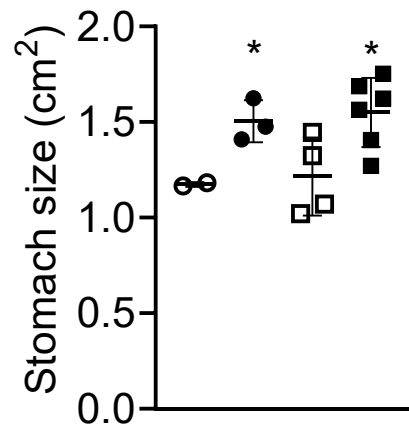
- WT Control
- ▲ WT Yoda1
- WT distended
- ◆ WT distended+GsMTx4
- TKO distended

Reduced ILC2s in tuft cell specific piezo1 KO mouse



→ 2 weeks of 20% chitin diet feeding

Dclk1-cre x piezo1^{flox/flox}
(Tuft cell specific Piezo1 KO)



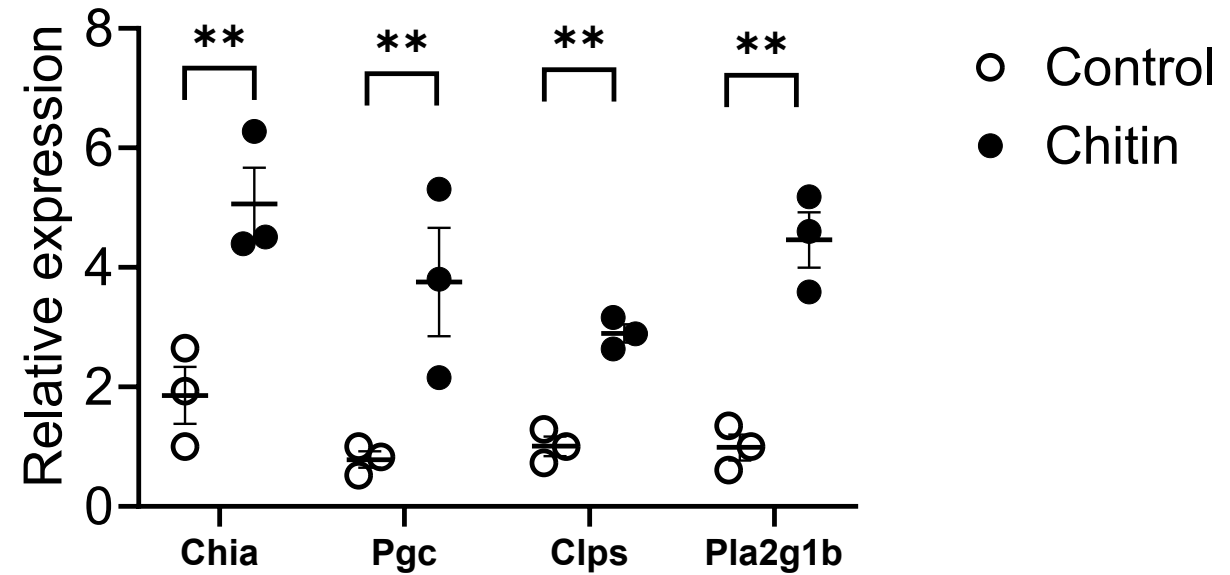
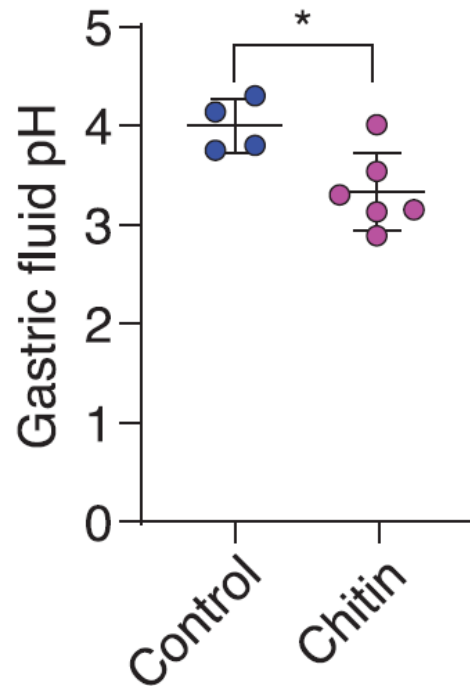
(unpublished data)

What is biological role of stretch sensing in stomach?



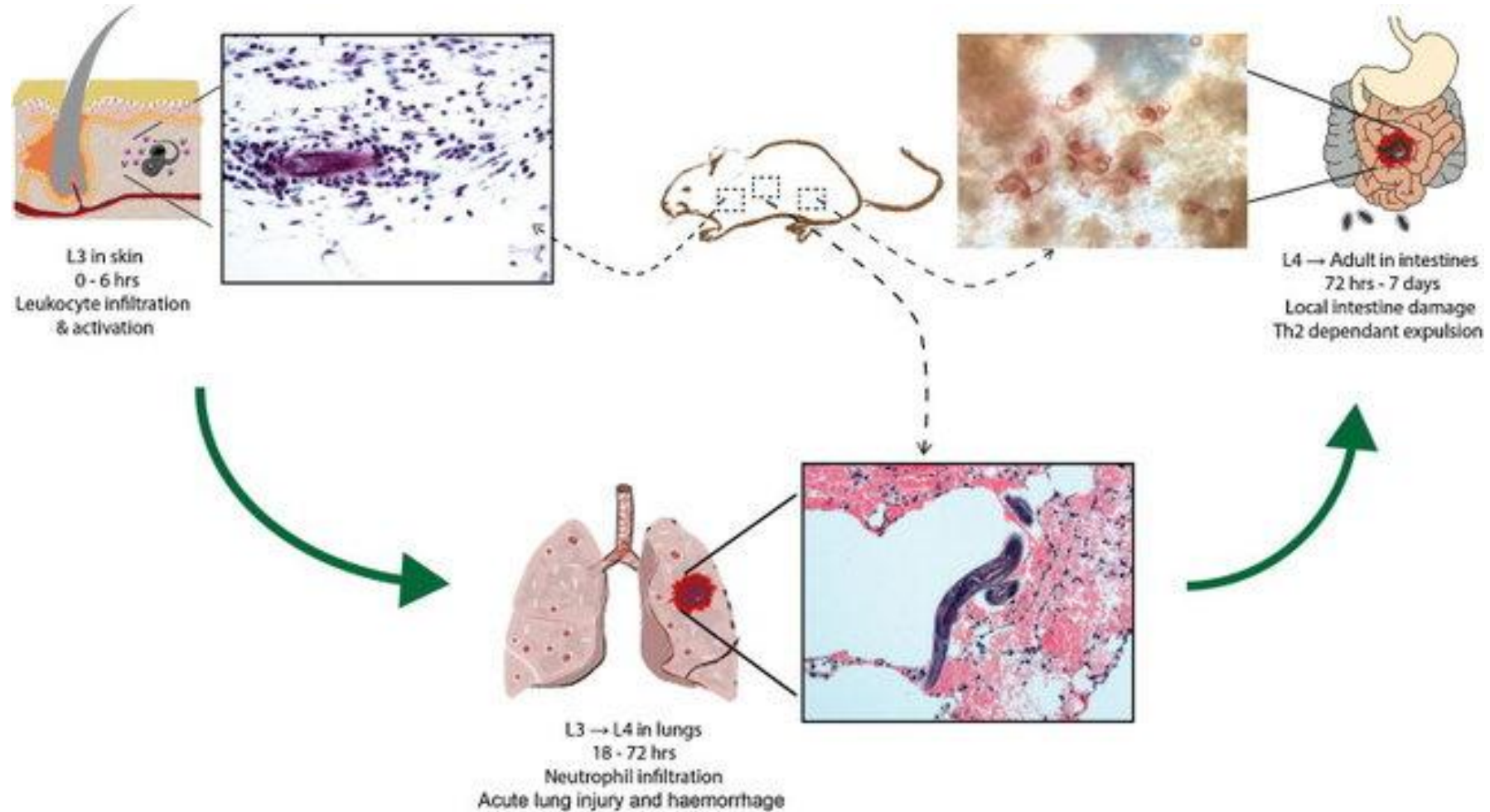
Hippocrates: Let Food Be The Medicine and Medicine Be The Food

Activated gastric ILC2s may promote digestive function

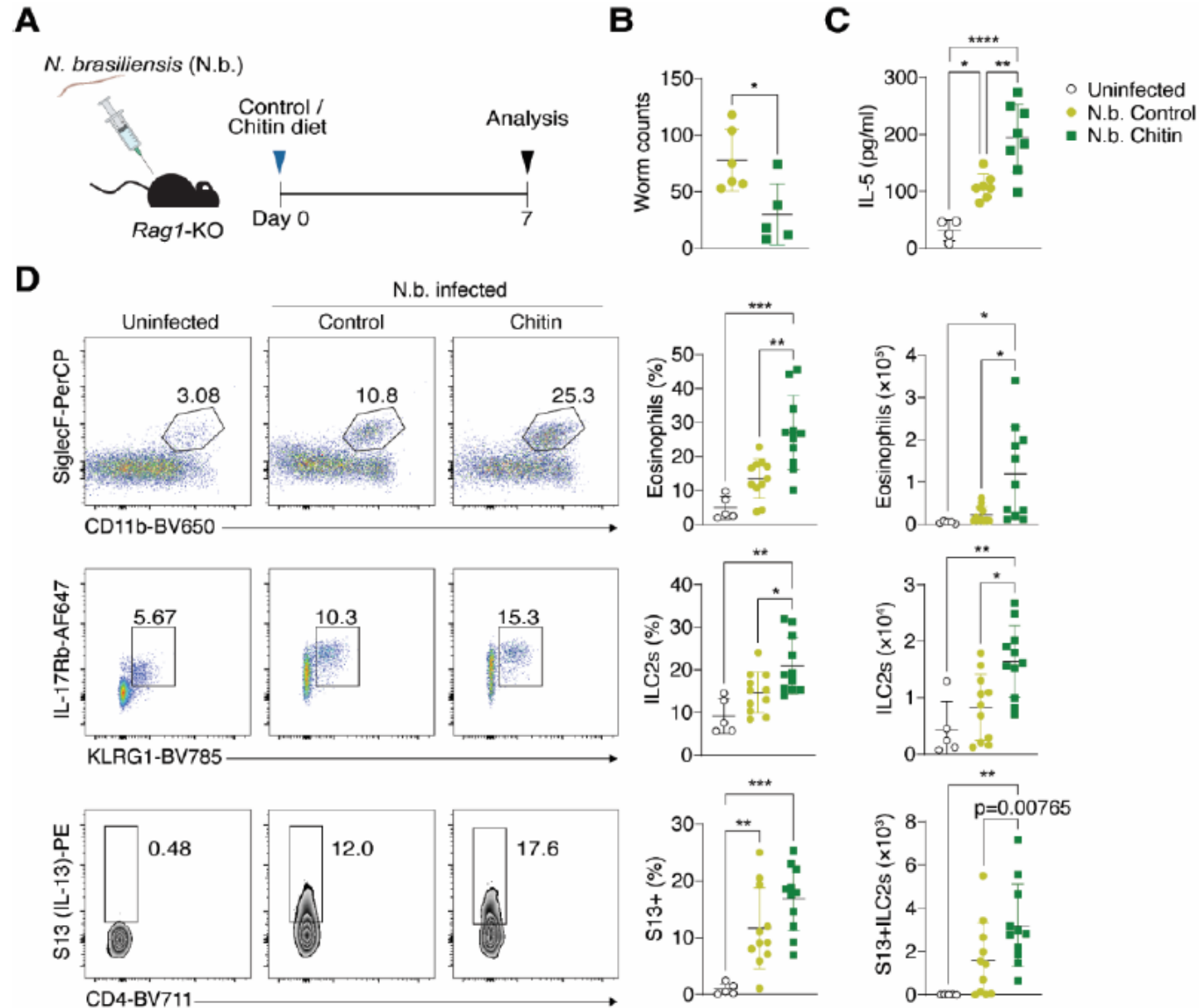


(unpublished data)

Any protective roles in intestinal infection model?



Stretch mediated innate type 2 activation reduces parasite burden

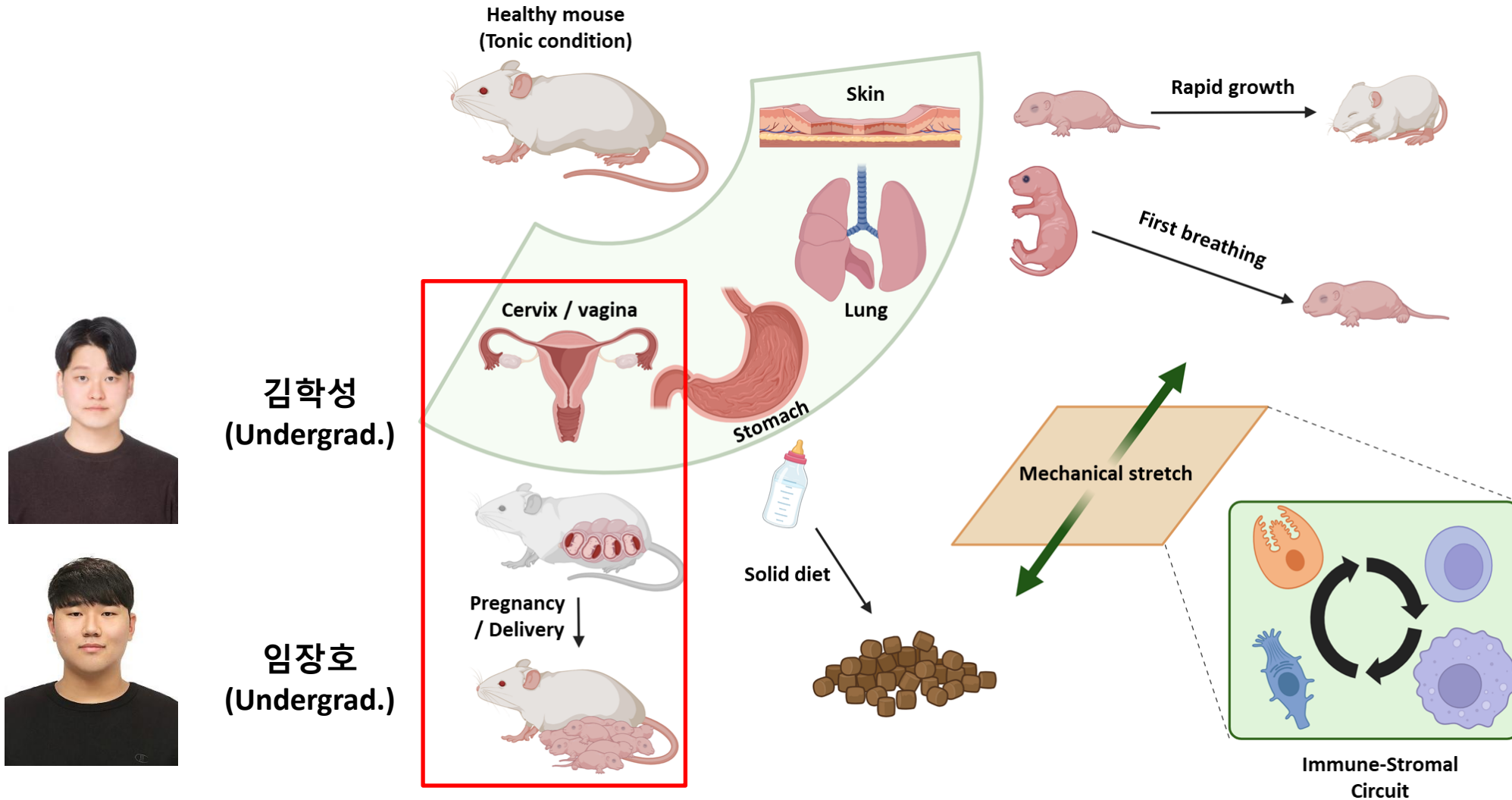


Conclusion

- Gastric tuft cell sensing mechanical stretch happened by feeding
- Gastric ILC2 matured by tuft cell
- Gastric tuft-ILC2 circuits enhance food bolus digestion
- Gastric tuft-ILC2 circuits enhance mucosal immune response against to helminth infection

Ongoing study about uterine stretch

Q. What is the tissue that most extensively experience mechanical stretch?

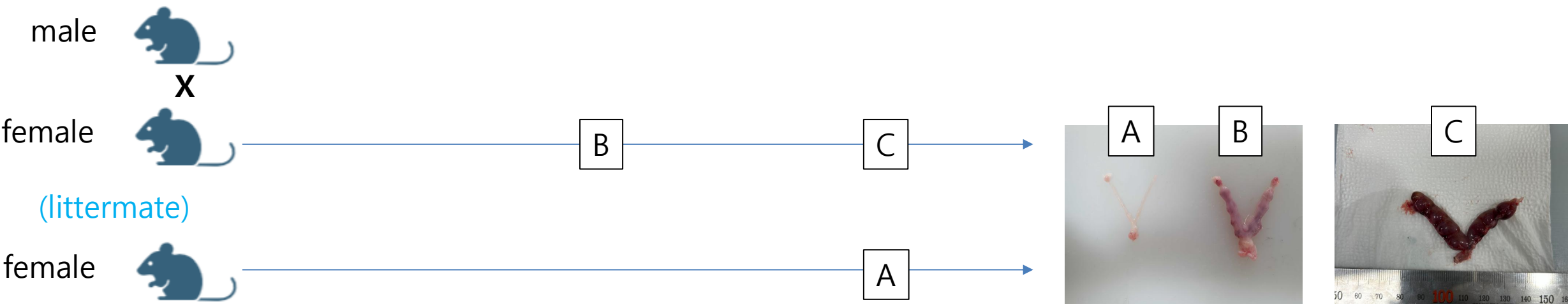


김학성
(Undergrad.)

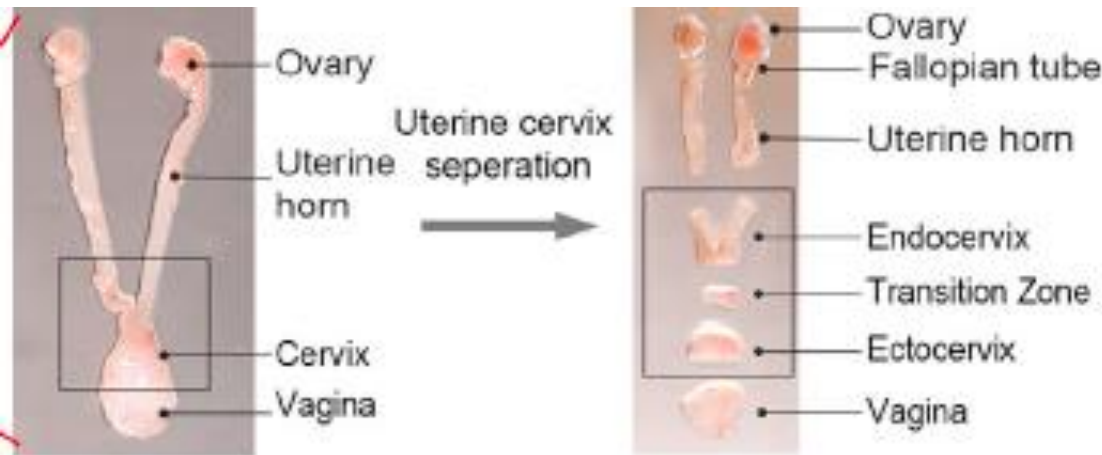


임장호
(Undergrad.)

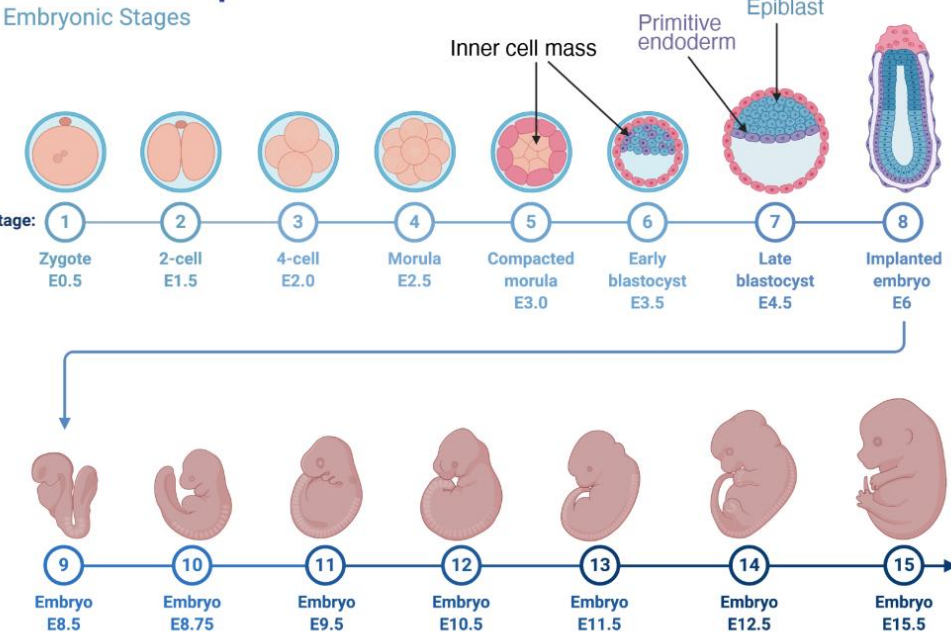
Experimental scheme



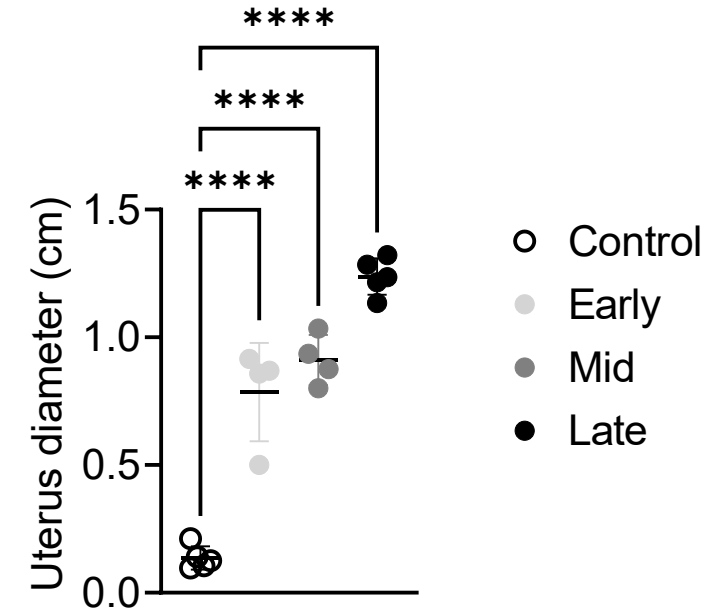
Sampling: Cervix / Uterine horn



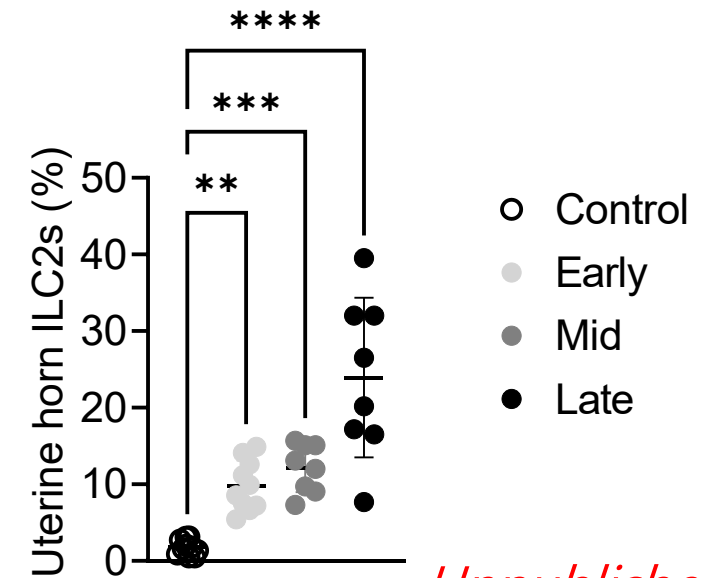
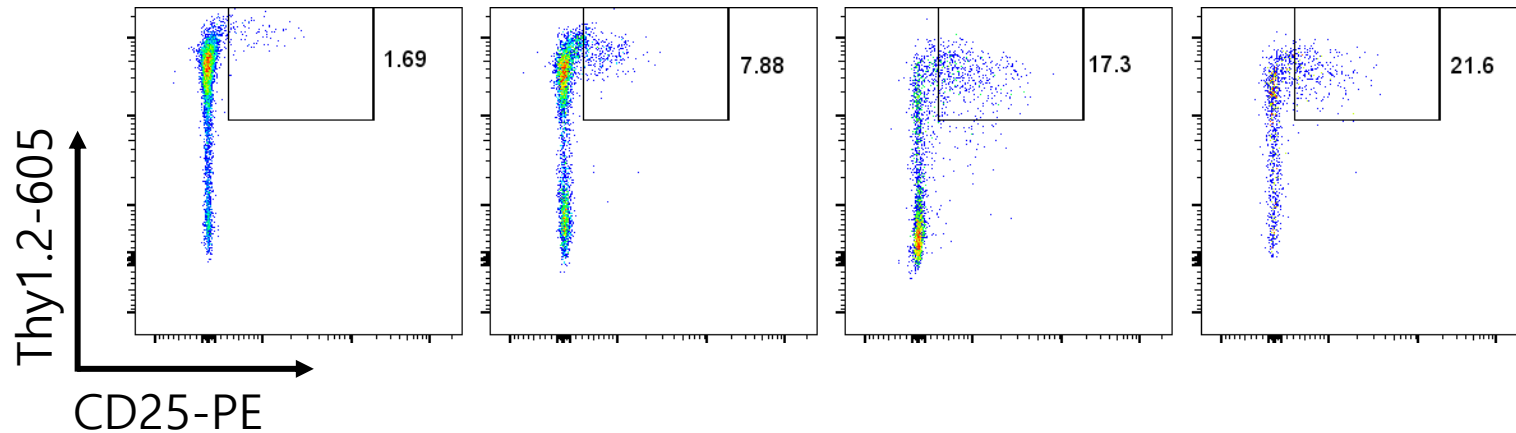
Mouse Development



Pregnancy induces uterine ILC2 activation



DAPI-CD45⁺CD11b⁻CD11c⁻CD4⁻CD3⁻



Unpublished

Is stretch matter? Or just sex-hormone mediated activation?

IL-33–Responsive Group 2 Innate Lymphoid Cells Are Regulated by Female Sex Hormones in the Uterus

Kathleen Bartemes,^{*,†} Chien-Chang Chen,^{*,†} Koji Iijima,^{*} Li Drake,^{*} and Hirohito Kita^{*,†}

2018 J Immunol

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

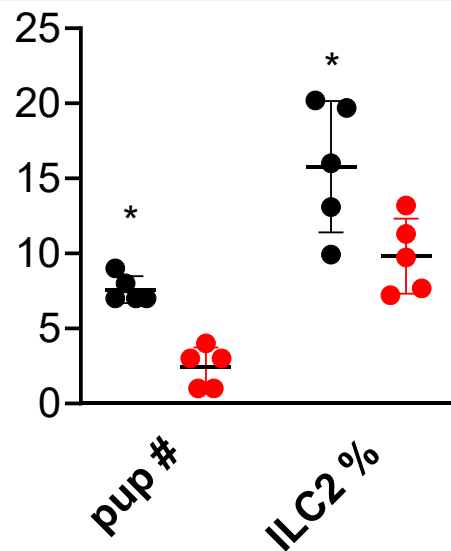
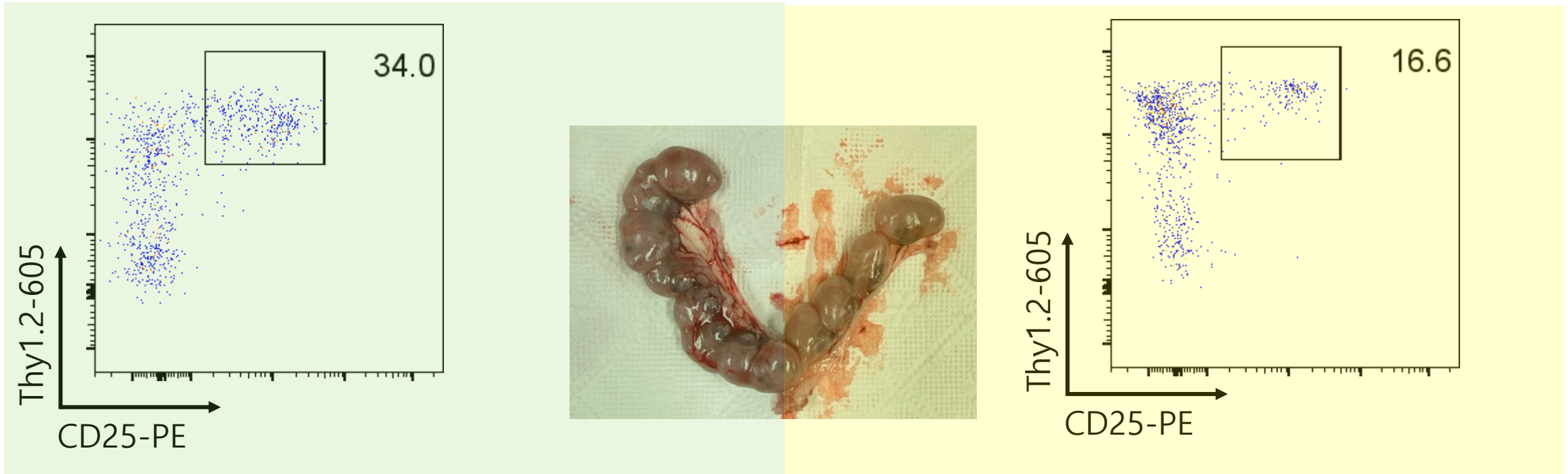
Allergy OFFICIAL JOURNAL OF THE EUROPEAN ACADEMY OF ALLERGY AND CLINICAL IMMUNOLOGY (EAACI) WILEY

Estrogen receptor- α signaling increases allergen-induced IL-33 release and airway inflammation

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2021 Allergy

Mechanical stretch may contribute to ILC2 activation



Positive correlation between number of pups and ILC2 %

What we studying

ILC2 based tissue circuits in biological events

[Mechanical stretch]

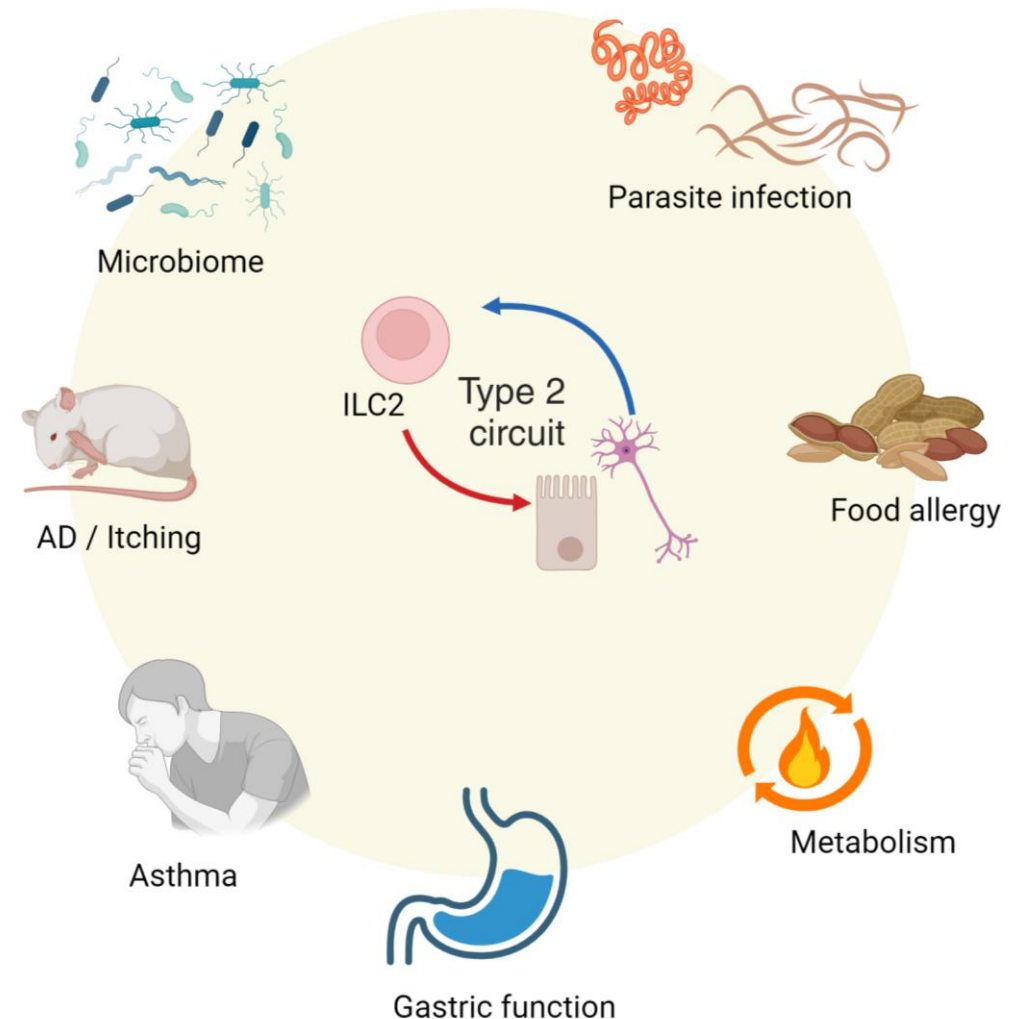
- First meal, and first breathing
- How immune – stromal circuit influence on female reproductive functions?

[Atopic March]

- How stress signal interaction in skin immune-stromal circuits contribute to atopic dermatitis?

[Neuro-immune crosstalk]

- Physiological role of ILC2s in enteric nerve system





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Acknowledgement



Van Dyken lab
at WashU
Steven J. Van Dyken
Intelly S. Lee
Haerin Jung
Yilin Wang

