The Kei-ichiro Maeda
Memorial T&C Award

Transcriptome-wide studies on mRNA tailing and investigation of stress responses in immune cells

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My academic journey from veterinary medicine to basic science

B.S./D.V.M.

Seoul National University
College of Veterinary Medicine

2005-2011

Ph.D.

Seoul National University
School of Biological Sciences

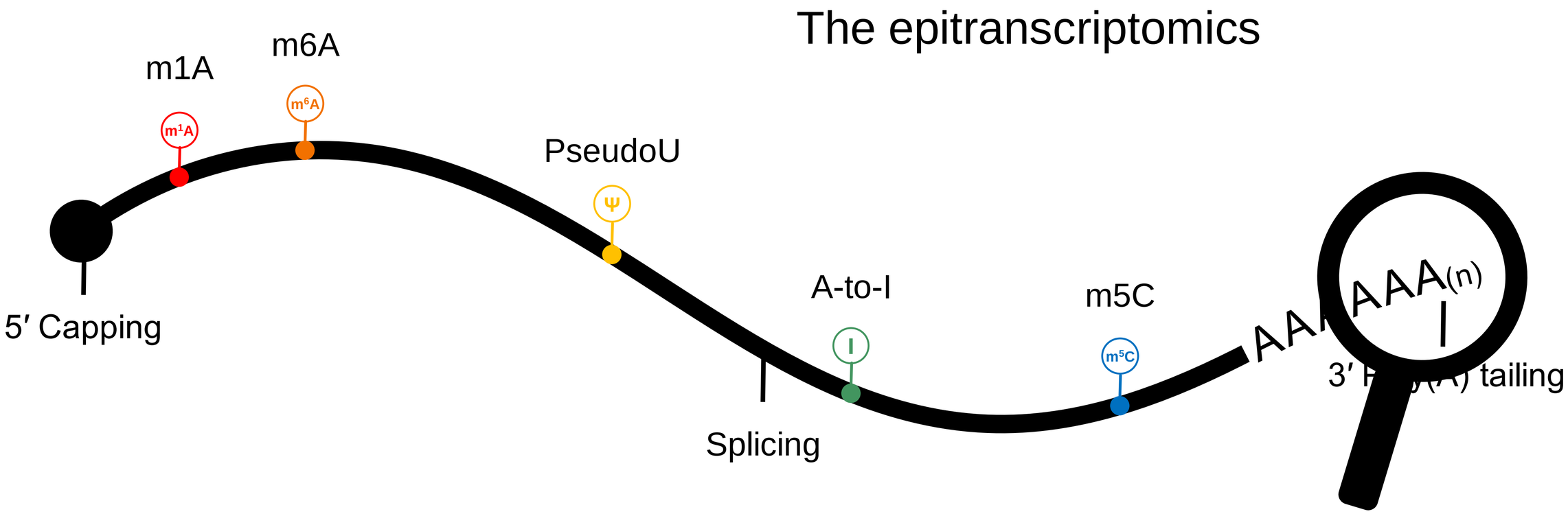
2011-2017

Postdoc

Yale School of Medicine
Department of Immunobiology

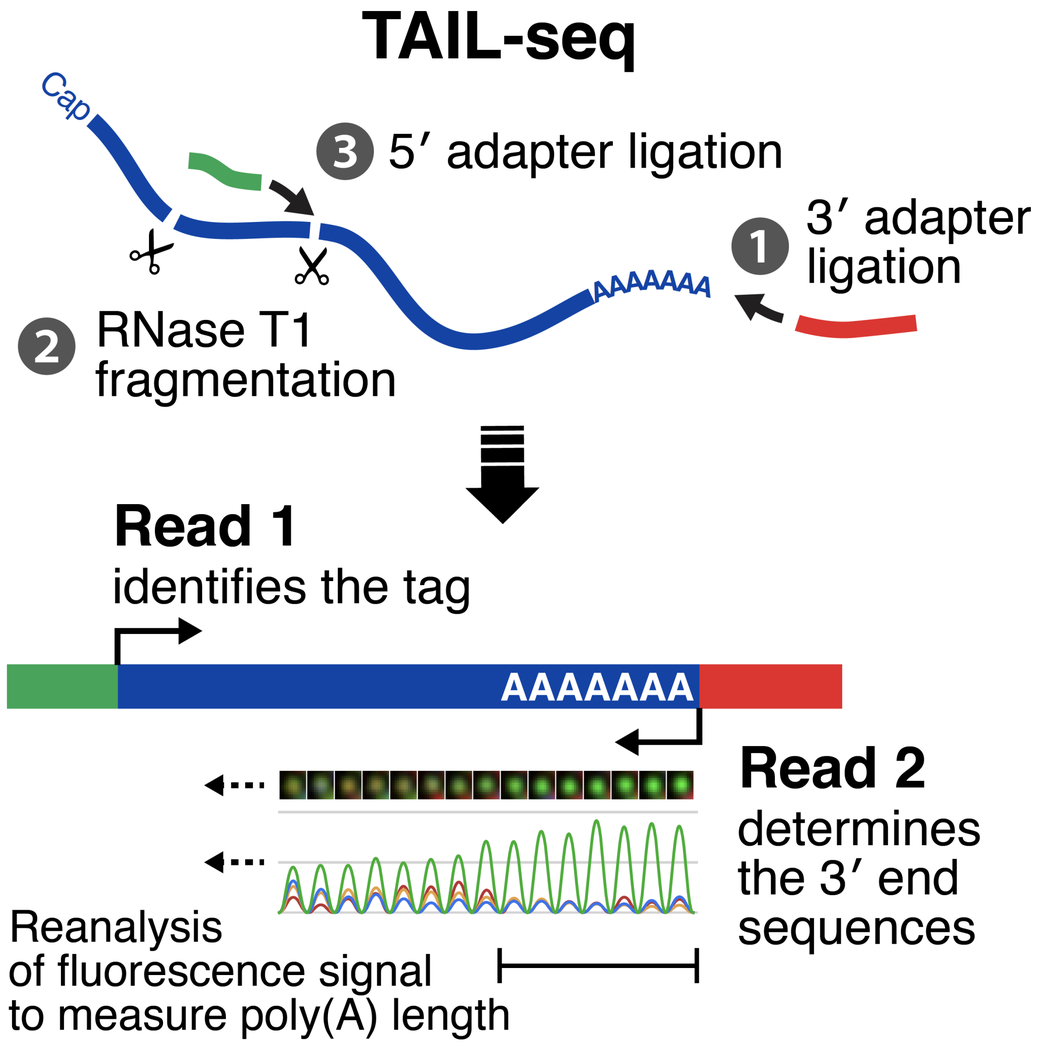
2017-2023

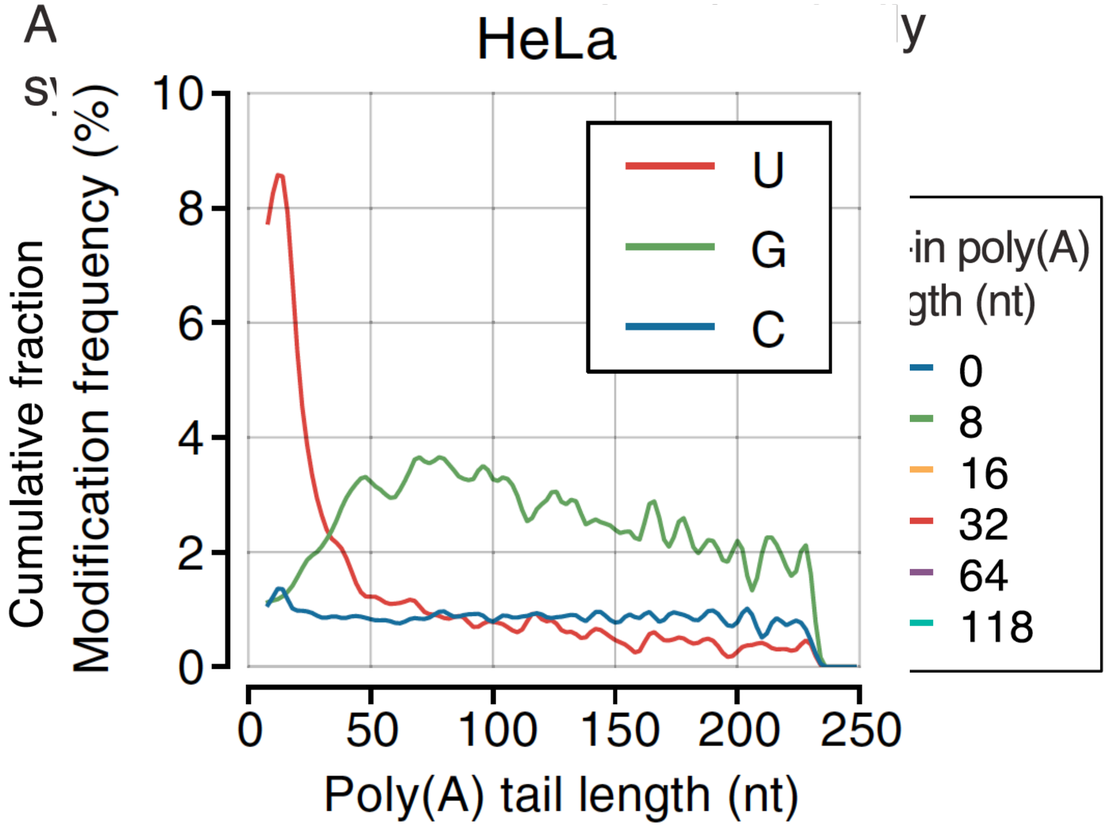
Post-transcriptional modifications of messenger RNA



Davalos et al., *Cell*, 2018

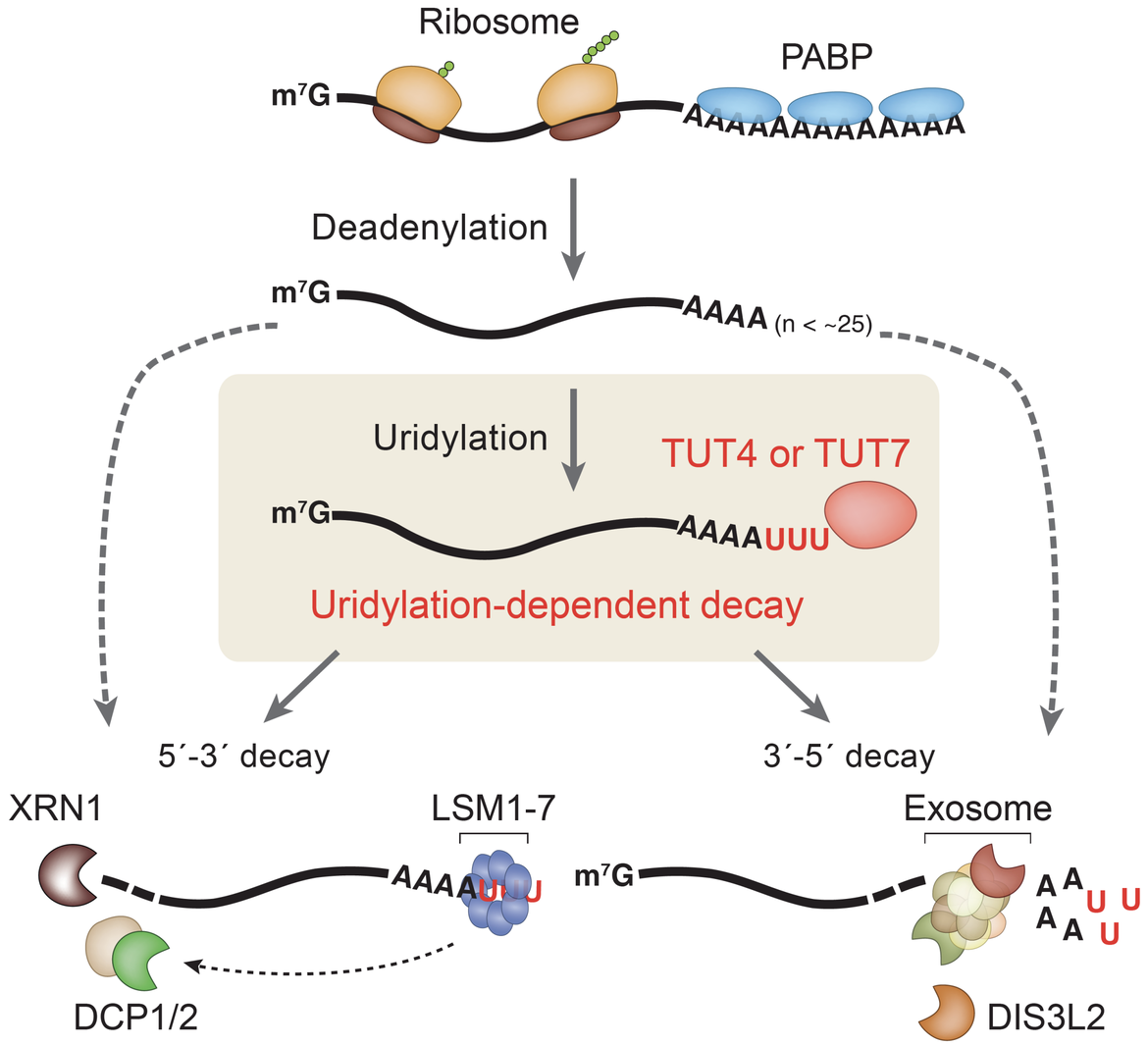
TAIL-seq revealed the transcriptome-wide landscape of RNA 3′ ends





Chang*, **Lim*** et al., ***Mol Cell***, 2014

Uridylation facilitates global mRNA degradation



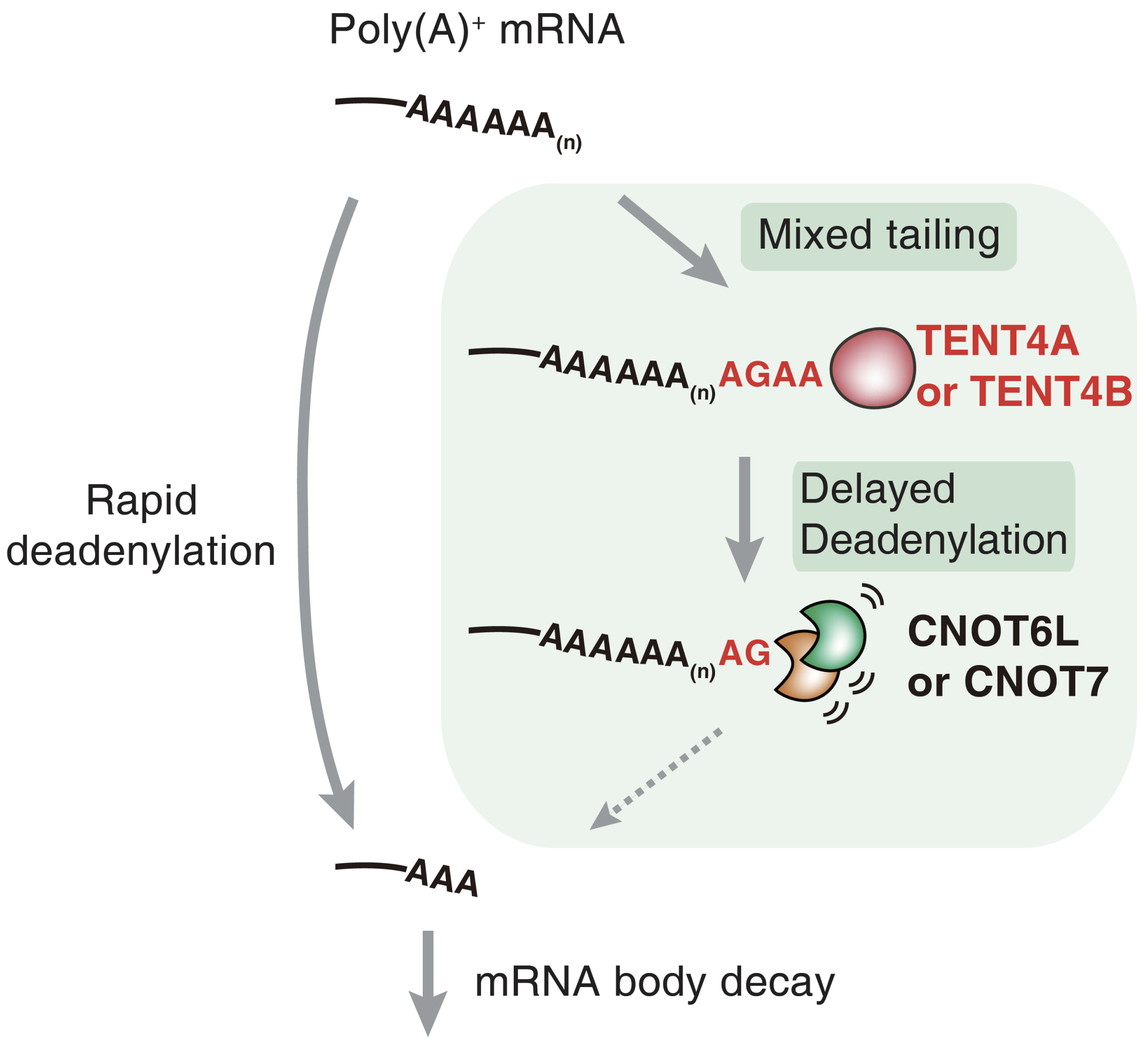
1. TUT4 and TUT7 specifically uridylate deadenylated mRNAs and thereby facilitate global mRNA decay.

2. mRNAs with short A tails (<~25 nt) lose PABP and instead gain a U-tail.

3. The oligo-U tail triggers mRNA decay by serving as a general mark that is recognized by downstream decay factors.

Lim*, Ha*, Chang* et al., ***Cell***, 2014

Mixed tailing shields mRNA from deadenylation



1. TENT4A/B add mixed tails (A >> G > C, U) to poly(A) mRNAs.

2. Non-adenosine residues slow down CNOT6L/7 deadenylases.

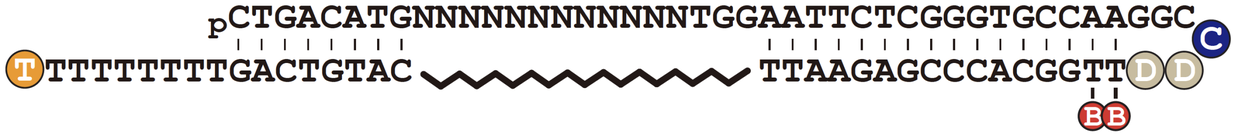
3. The mixed tail protects and stabilizes mRNAs from deadenylation.

Lim*, Kim*, Lee* et al., ***Science***, 2018

mTAIL-seq accurately measures poly(A) tail length with low input samples

TAIL-seq 3′ adaptor

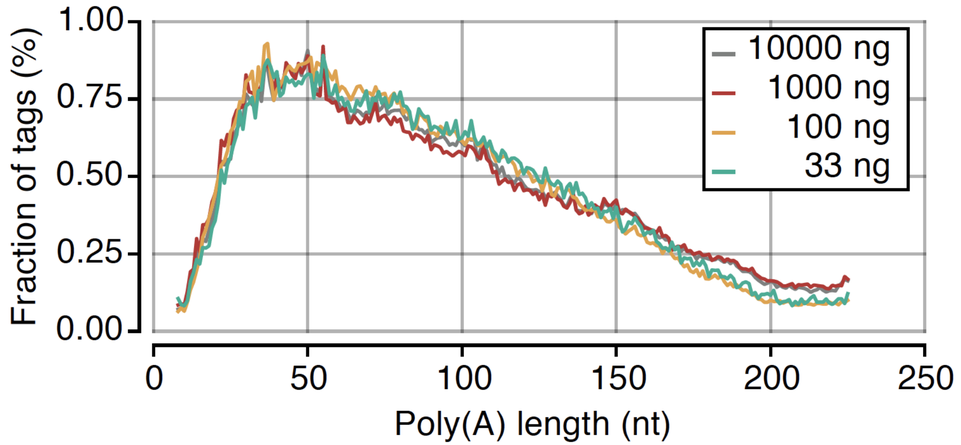
mTAIL-seq 3′ adaptor (hairpin)



B Biotin Spacer T Inverted dT (3′-3′ linkage)

C C3 spacer phosphoramidite D 1′, 2′ -Dideoxyribose (abasic site)

Global poly(A) distribution



→ Fly oocytes and embryos

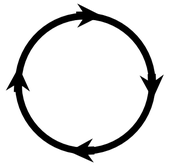
→ Dynamic poly(A) tail regulation in oocyte-to-embryo development

Lim*, Lee* et al., ***Genes Dev***, 2016

TAIL-seq and mTAIL-seq have been applied to various biological studies

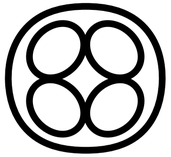
mRNA metabolism
(Deadenylation, decay, and translation)

Lima et al., *Nat Str Mol Biol*, 2017
Yi*, Park* et al., *Mol Cell*, 2018
Eisen*, Eichhorn*, Subtelny* et al., *Mol Cell*, 2020
Xiang and Bartel, *eLife*, 2021



Cell cycle regulation

Park*, Yi*, Kim* et al., *Mol Cell*, 2016
Liu et al., *iScience*, 2020

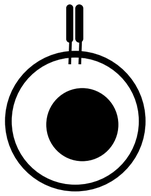


Development
(Oogenesis and embryogenesis)

Lim*, Lee* et al., *Genes Dev*, 2016
Morgan*, Much* et al., *Nature*, 2017
Chang*, Yeo* et al., *Mol Cell*, 2018

Viral infection

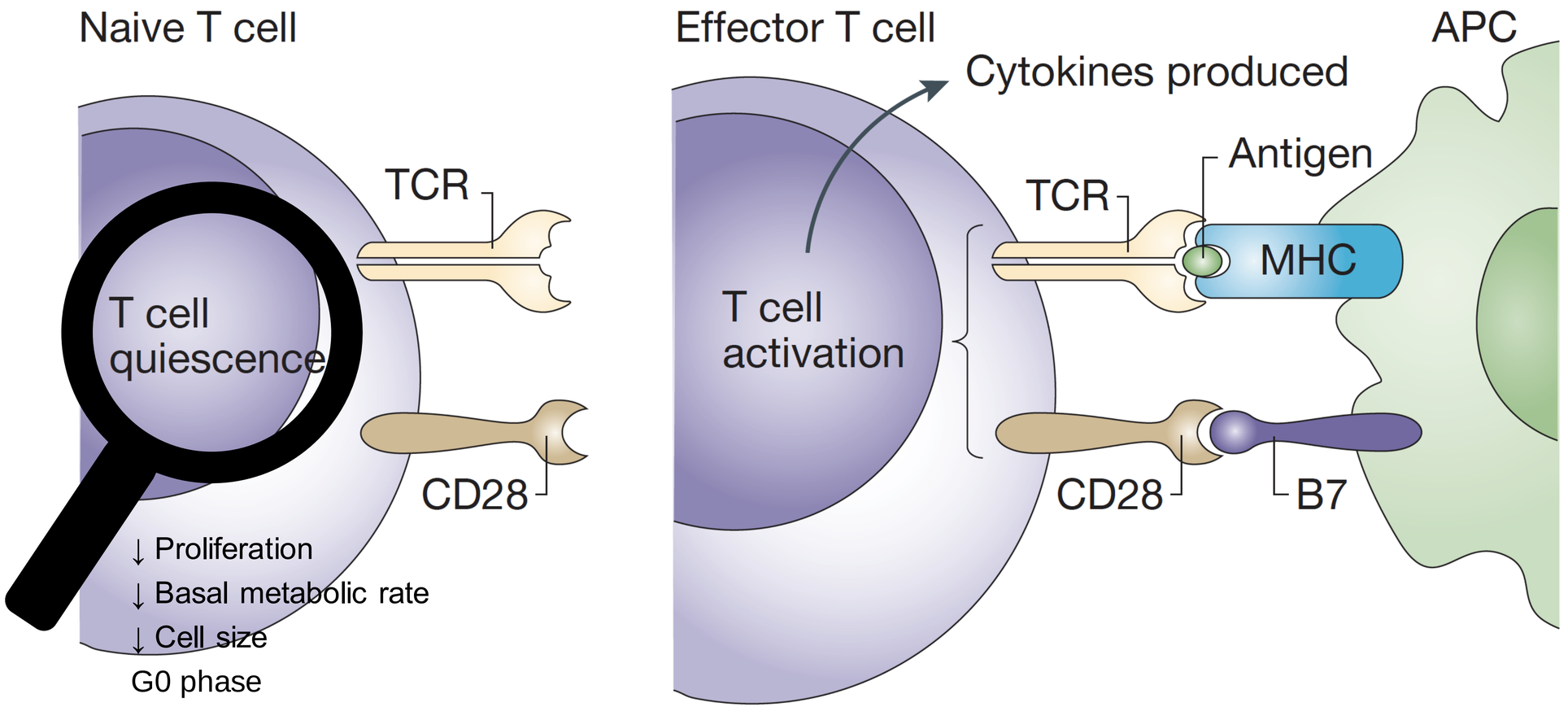
Batra*, Stark* et al., *Nat Str Mol Biol*, 2016
Kim*, Lee*, Jung*, Yeo* et al., *Nat Str Mol Biol*, 2020



T cell quiescence

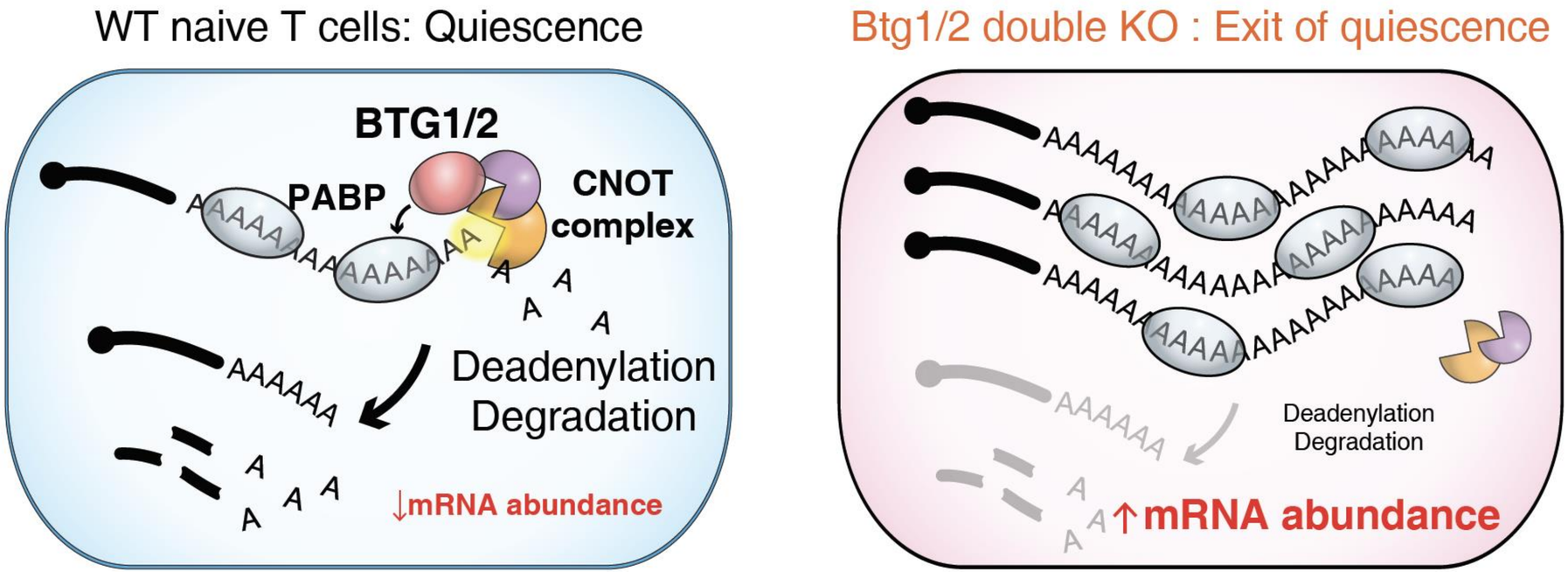
Hwang*, **Lim*** et al., ***Science***, 2020

T cells maintain quiescence in the absence of activation stimuli



Modified from Sharma et al., *Nat Rev Cancer*, 2011

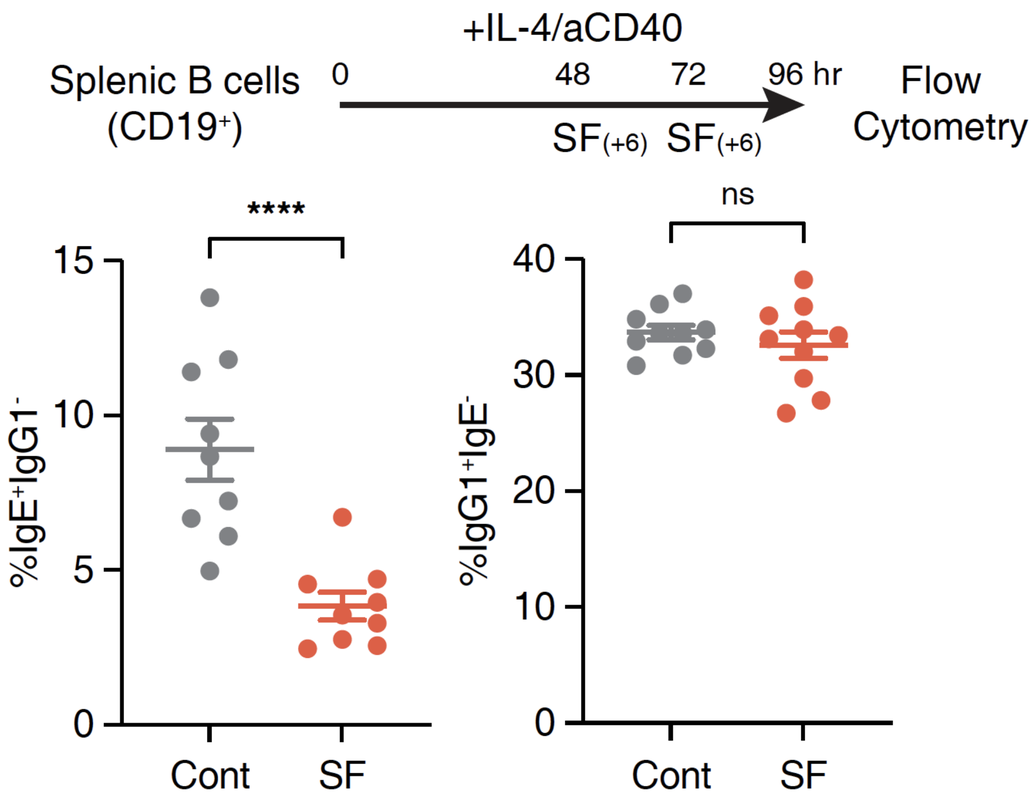
mRNA destabilization by BTG1/2 maintains T cell quiescence

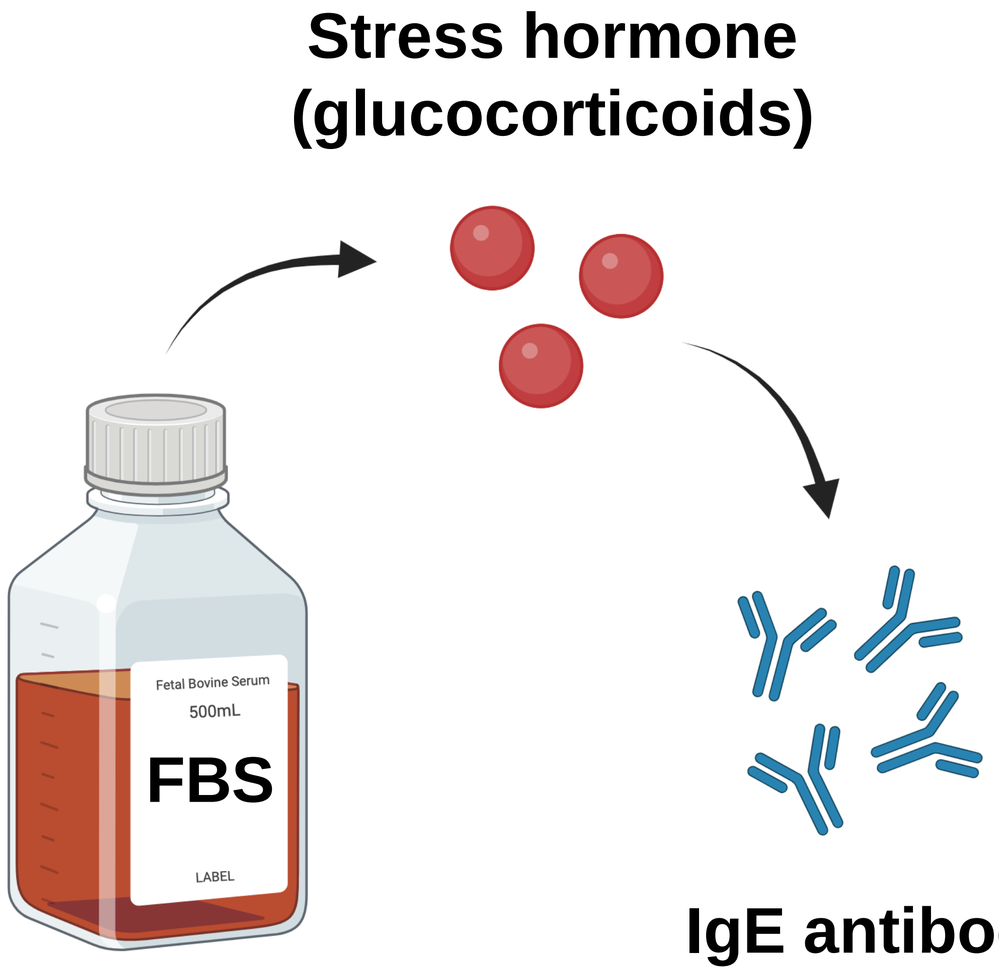


1. BTG1/2 promote global mRNA deadenylation and degradation in naive T cells.
2. Loss of Btg1/2 results in exit of T cell quiescence by increasing global mRNA levels.
3. Active mRNA turnover might be a crucial feature for maintaining quiescence.

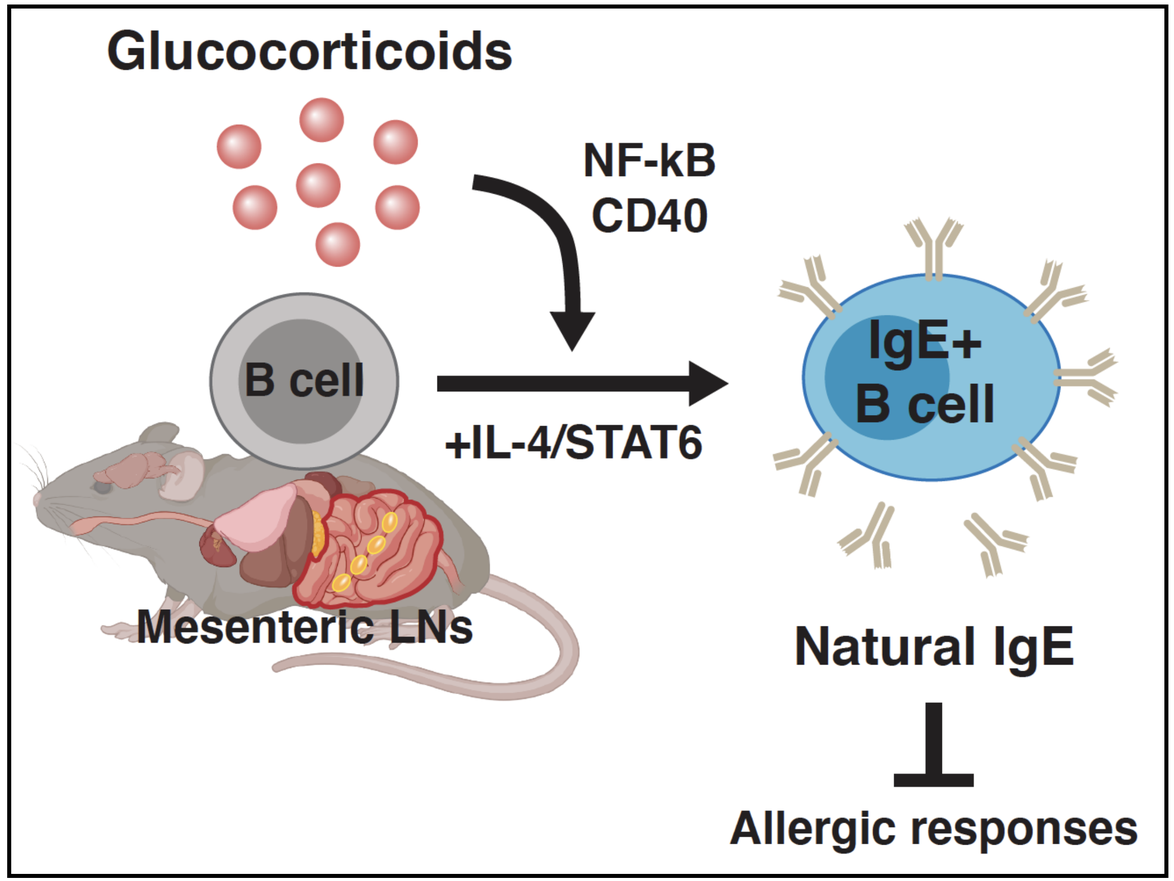
Hwang*, **Lim*** et al., ***Science***, 2020

Transient serum starvation selectively decreases IgE switching





Stress hormones, glucocorticoids, induce natural IgE



1) Glucocorticoids induce natural IgE both *in vivo* and *ex vivo* without antigenic challenge.

2) Glucocorticoids reinforce CD40 signaling and are dependent on IL-4/STAT6.

3) Natural IgE-producing B cells are localized in mLNs *in vivo*.

4) Natural IgE induced by glucocorticoids may have a protective role in preventing allergic reactions.

Lim*, Lin*, Hong* et al., ***J Exp Med***, 2022

Future plans in the college of veterinary medicine

I will investigate how cells or animals adapt to stress conditions.

1. Animals have a variety of digestive systems. I aim to understand how immune cells maintain homeostasis, especially in the gut. I am interested in the role of immune cells when gut homeostasis is perturbed, such as dysbiosis or food poisoning.

2. In response to stress, some animals exhibit a highly stress-resistant state, like hibernation or dormancy. I am interested in the molecular mechanisms how cells or animals cope with extreme environmental conditions.

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