Computational Modeling of Gut-Bone Axis and Implications of Butyrate Treatment on Osteoimmunology

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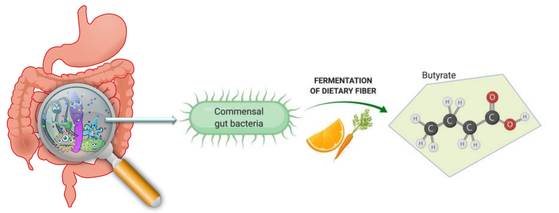
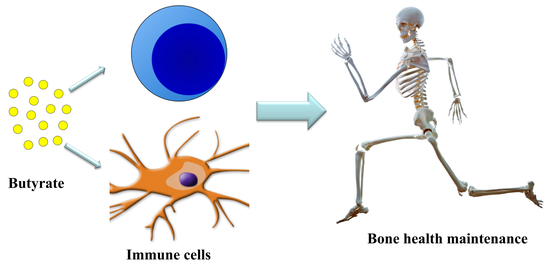
Introduction

Butyrate is a short chain fatty acid produced by gut microbiota



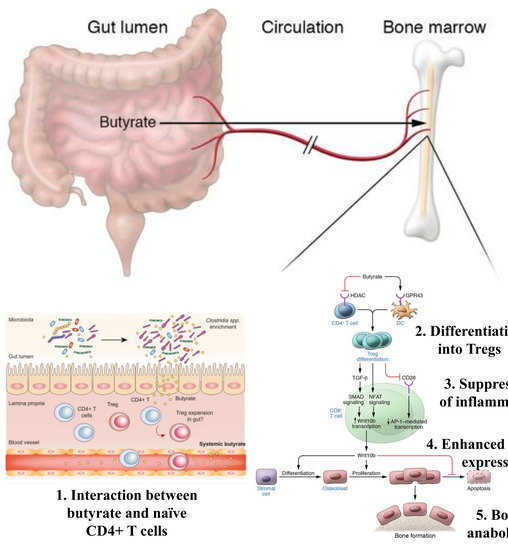
https://immunobites.com/gut-out-of-here-how-gut-microbiome-can-enhance-immune-response/

Interaction between butyrate and immune cells play a pivotal role in the maintenance of bone



- Butyrate treatment increases bone volume
- Probiotic LGG and butyrate supplements increase local and systemic butyrate
- Butyrate is a possible treatment for bone diseases (e.g., osteoporosis & osteoarthritis)

Mechanism of butyrate inducing bone anabolism



Zaiss, et al. J Clin Invest, 2019 & Begka, et al. Immunity, 2018

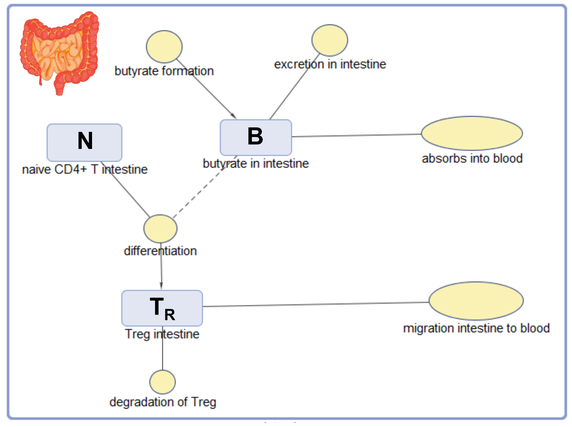
- Therapeutic benefit of butyrate in bone anabolism remains poorly understood

Purpose

- Create a multi-compartment PBPK model to track and quantify effects of butyrate on Tregs in gut, blood, and bone
- Connect Wnt10b expression enhanced by Tregs to bone remodeling

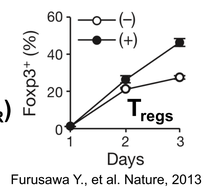
Intestine

- Butyrate differentiates naïve T cells to Tregs
- Constant formation and supply of butyrate
- Butyrate and Tregs migrate to blood

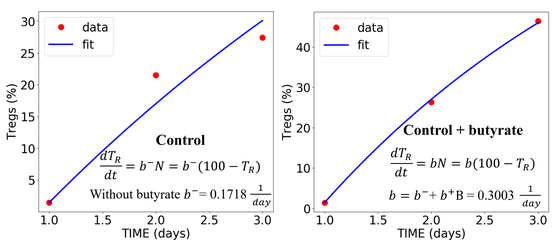


In vitro data shows butyrate enhances differentiation of naïve T cells into Tregs (Foxp3+)

- In vitro differentiation of naïve T cells without (-) and with (+) butyrate (B = 100 μM)
- Total cell population is constant (Total 100% = N + T_R)
- Activity, γ, will be reduced in vivo



Furusawa Y., et al. Nature, 2013

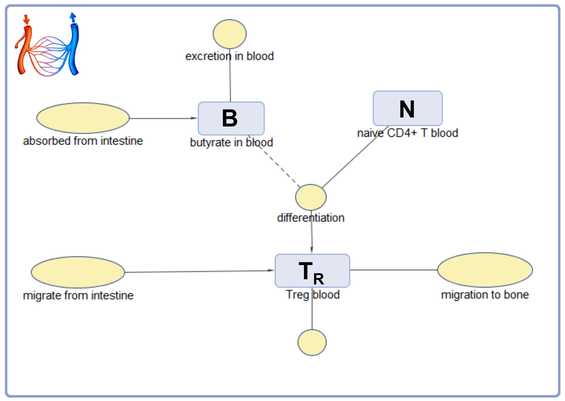


$$\textit{in vitro}: \frac{dT_R}{dt} = b^-N + b^+BN$$

$$\textit{in vivo}: \frac{dT_R}{dt} = \gamma(b^-N + b^+\mathrm{BN})$$

Blood

- Butyrate absorbs in blood and differentiates naïve T cells to Tregs
- Tregs migrate to bone



In vivo experimental data reveals biodistribution of butyrate and Tregs

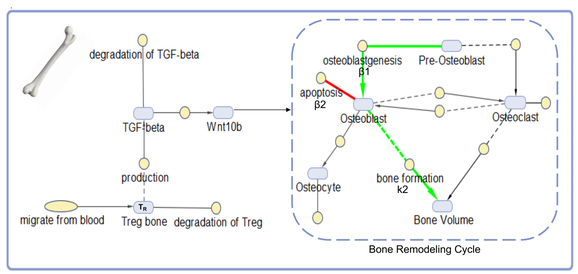
Experimental data after 4 weeks of LGG dosage in mouse (Tyagi, et al. Immunity, 2018)

	Control	LGG	Control	LGG
Butyrate	Small Intestine (SI), μM		Serum Blood, μM	
	0.24 ± 0.03	0.42 ± 0.07	0.35 ± 0.07	0.64 ± 0.08
Regulatory T cells	Spleen (% CD4+ T cell)		Bone (% CD4+ T cell)	
	13 ± 0.6	16 ± 0.4	42 ± 1	48 ± 2

- Absorption rate, migration rate, and activity are estimated based on these in vivo results

Bone

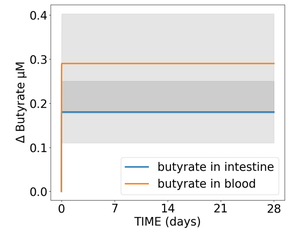
Tregs promote bone anabolism via Wnt10b

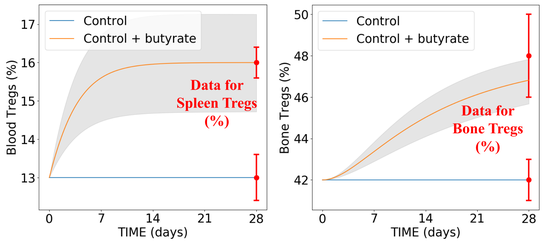


- Tregs produce TGF-β, which increases Wnt10b
- Wnt10b increases osteoblast production (β1) and rate of bone formation (k2)
- Wnt10tb decreases osteoblast apoptosis (β2)

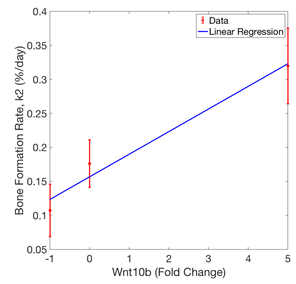
Results

- We consider change of butyrate concentration in small intestine with error bar (shaded area)
- We assume immediate formation of butyrate, but linear or periodic increase is also possible





- At homeostasis, ΔB = 0 μM & Tregs in blood are 13% and bone are 42% of total cells (N + T_R)
- 3% increase of Tregs in blood and 5% increase of Tregs in bone is observed with ΔB = 0.18 μM change of butyrate in intestine



- k2 is estimated linearly for mice using bone formation rate data

$$k_2 = (0.0332\mathrm{Wnt10b\ fold\ change}) + 0.1568$$

Impacts

- Give insight on pharmacokinetics of butyrate, Tregs, and their contributions to modulating bone formation
- Understand how butyrate modification could be used as a possible treatment for different pathological conditions relating to bone

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