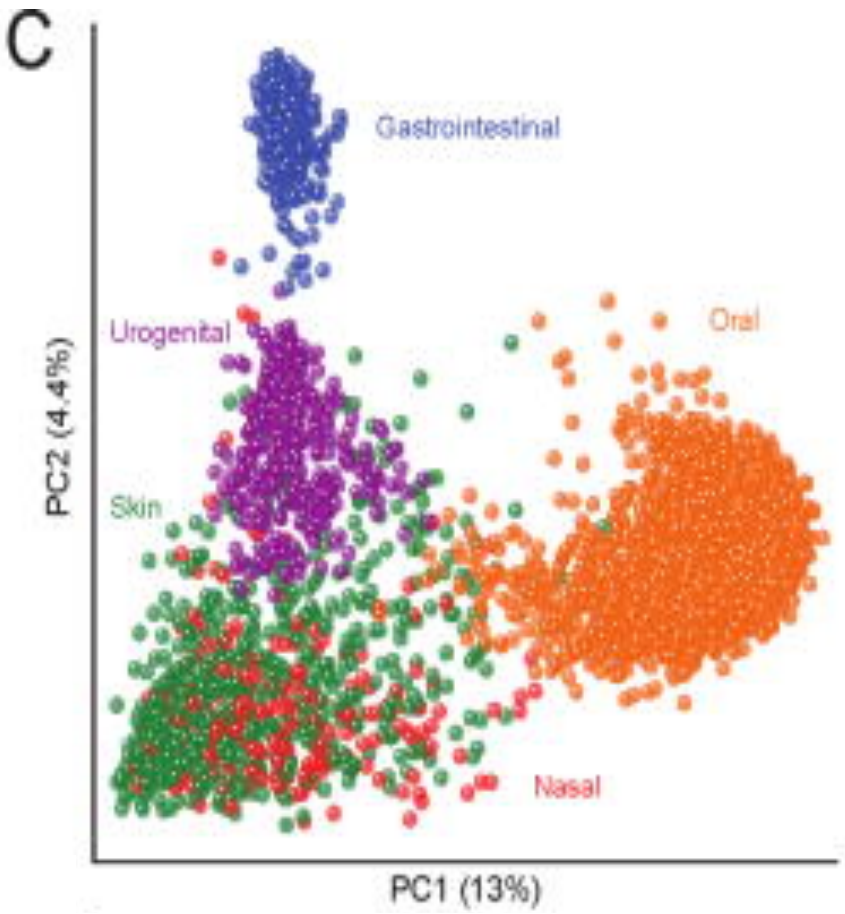
20.109
Laboratory Fundamentals in Biological Engineering

Module 1

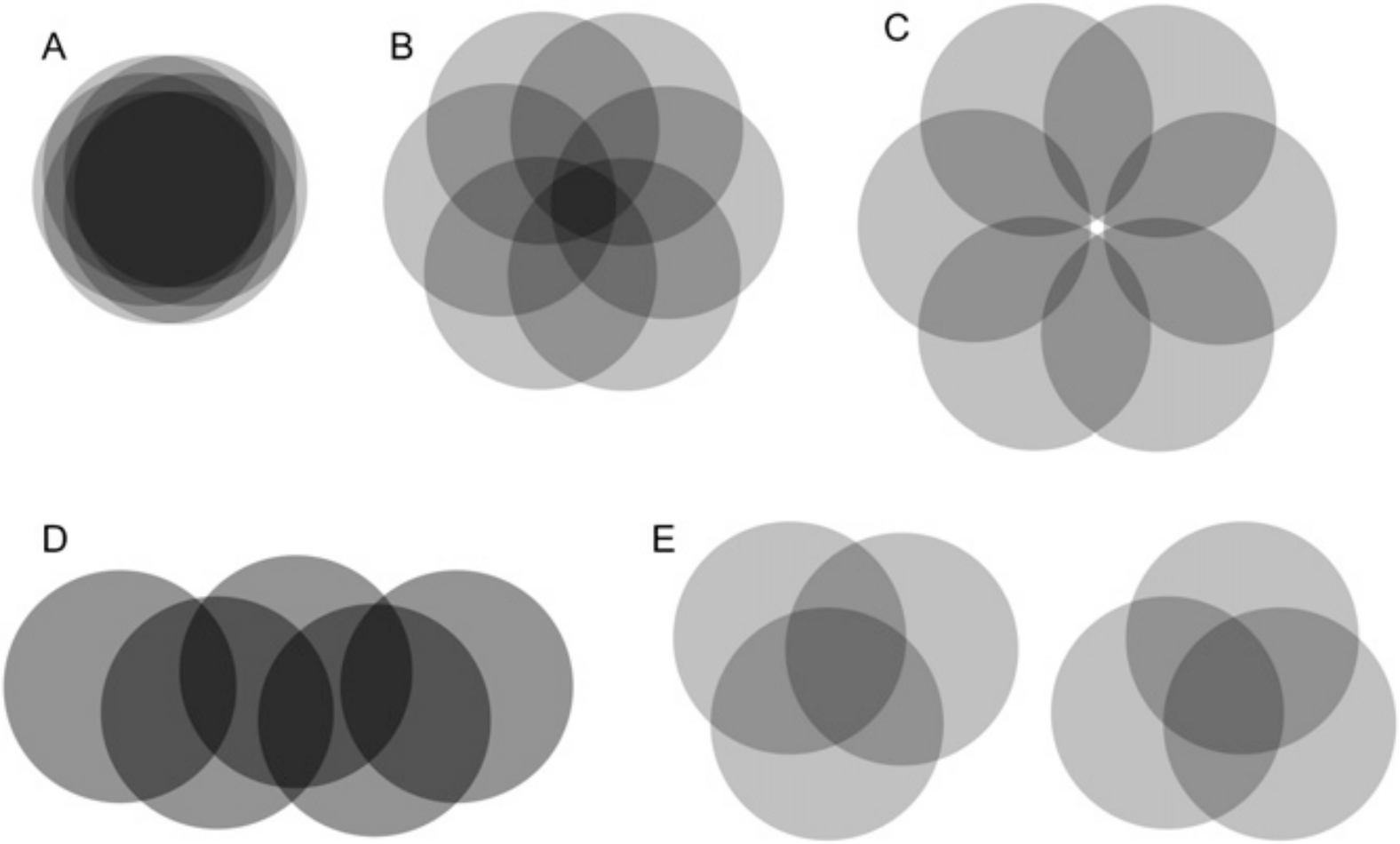
Nucleic Acids

Lecture 5

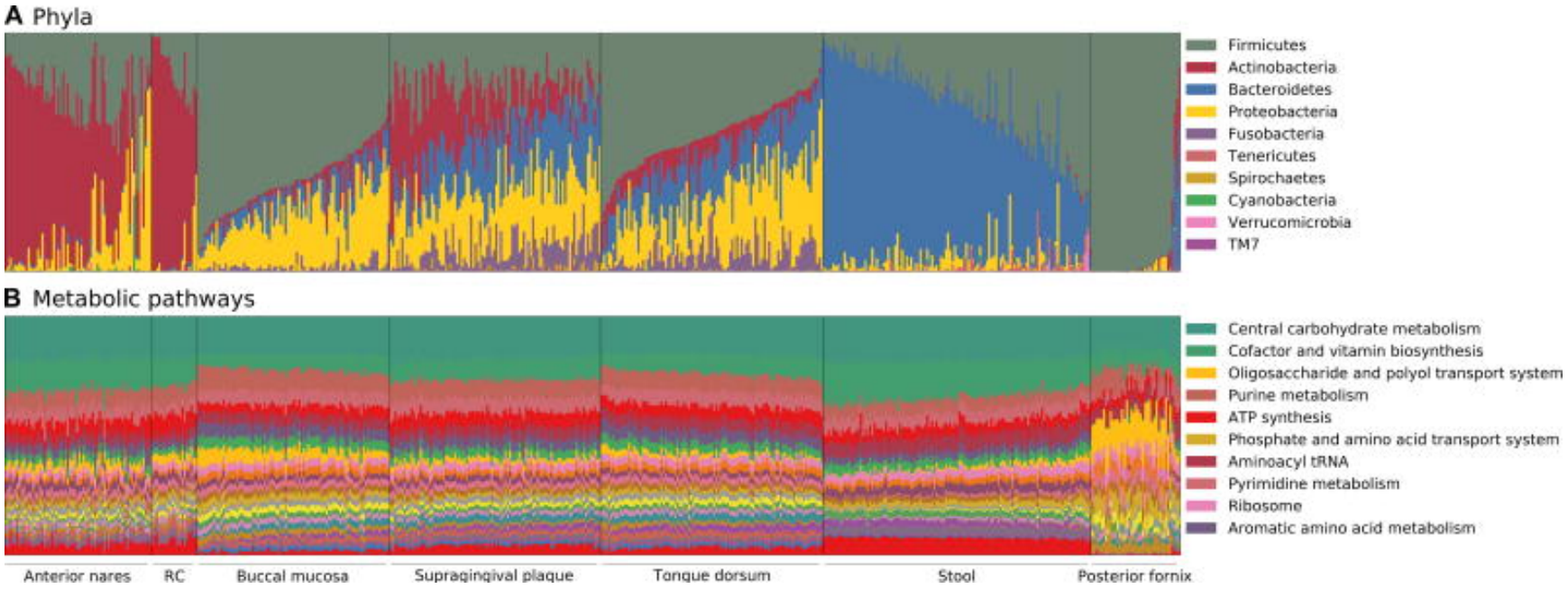
J. Runstadler


C
Gastrointestinal
Urogenital
Oral
Skin
Nasal
PC2 (4.4%)
PC1 (13%)

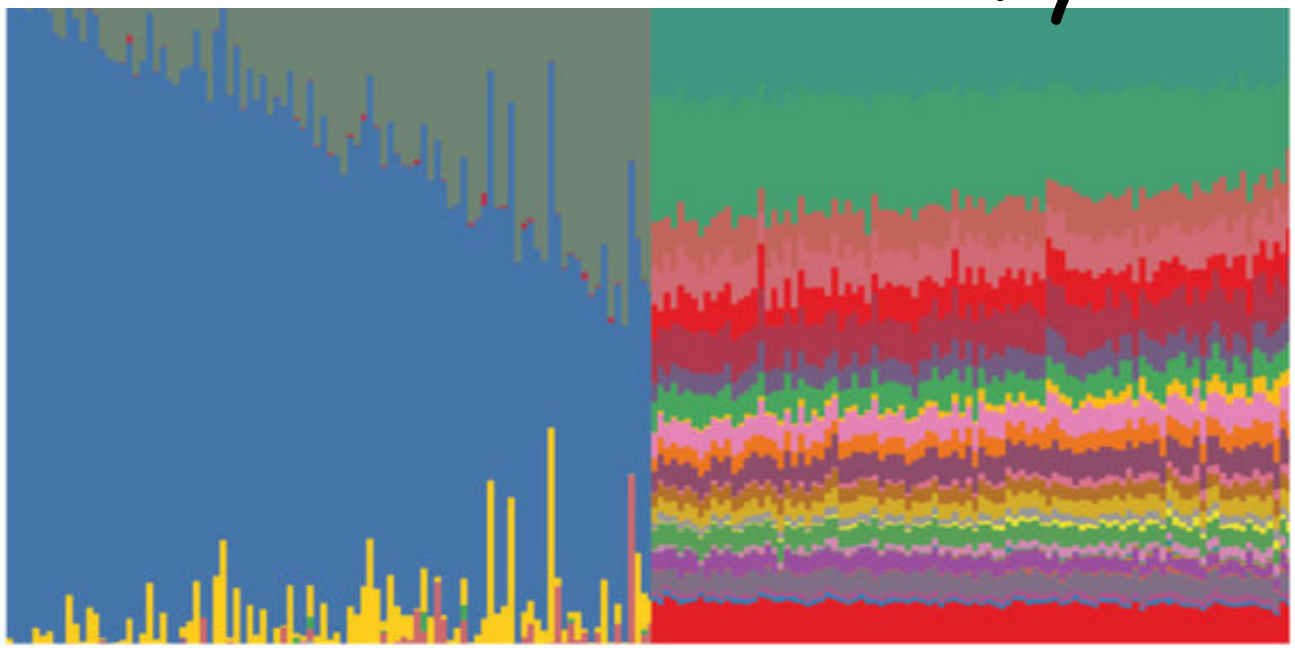
Models of a core microbiome



Hamady and Knight, 2009


A Phyla
Firmicutes
Actinobacteria
Bacteroidetes
Proteobacteria
Fusobacteria
Tenericutes
Spirochaetes
Cyanobacteria
Verrucomicrobia
TM7
B Metabolic pathways
Central carbohydrate metabolism
Cofactor and vitamin biosynthesis
Oligosaccharide and polyol transport system
Purine metabolism
ATP synthesis
Phosphate and amino acid transport system
Aminoacyl tRNA
Pyrimidine metabolism
Ribosome
Aromatic amino acid metabolism
Anterior nares
RC
Buccal mucosa
Supragingival plaque
Tongue dorsum
Stool
Posterior fornix

Function is more relevant than taxonomy



Firmicutes
Actinobacteria
Bacteroidetes
Proteobacteria
Fusobacteria
Tenericutes
Spirochaetes
Cyanobacteria
Verrucomicrobia
TM7

Central carbohydrate metabolism
Cofactor and vitamin biosynthesis
Oligosaccharide and polyol transport system
Purine metabolism
ATP synthesis
Phosphate and amino acid-transport system
Aminoacyl transfer RNA
Pyrimidine metabolism
Ribosome
Aromatic amino-acid metabolism

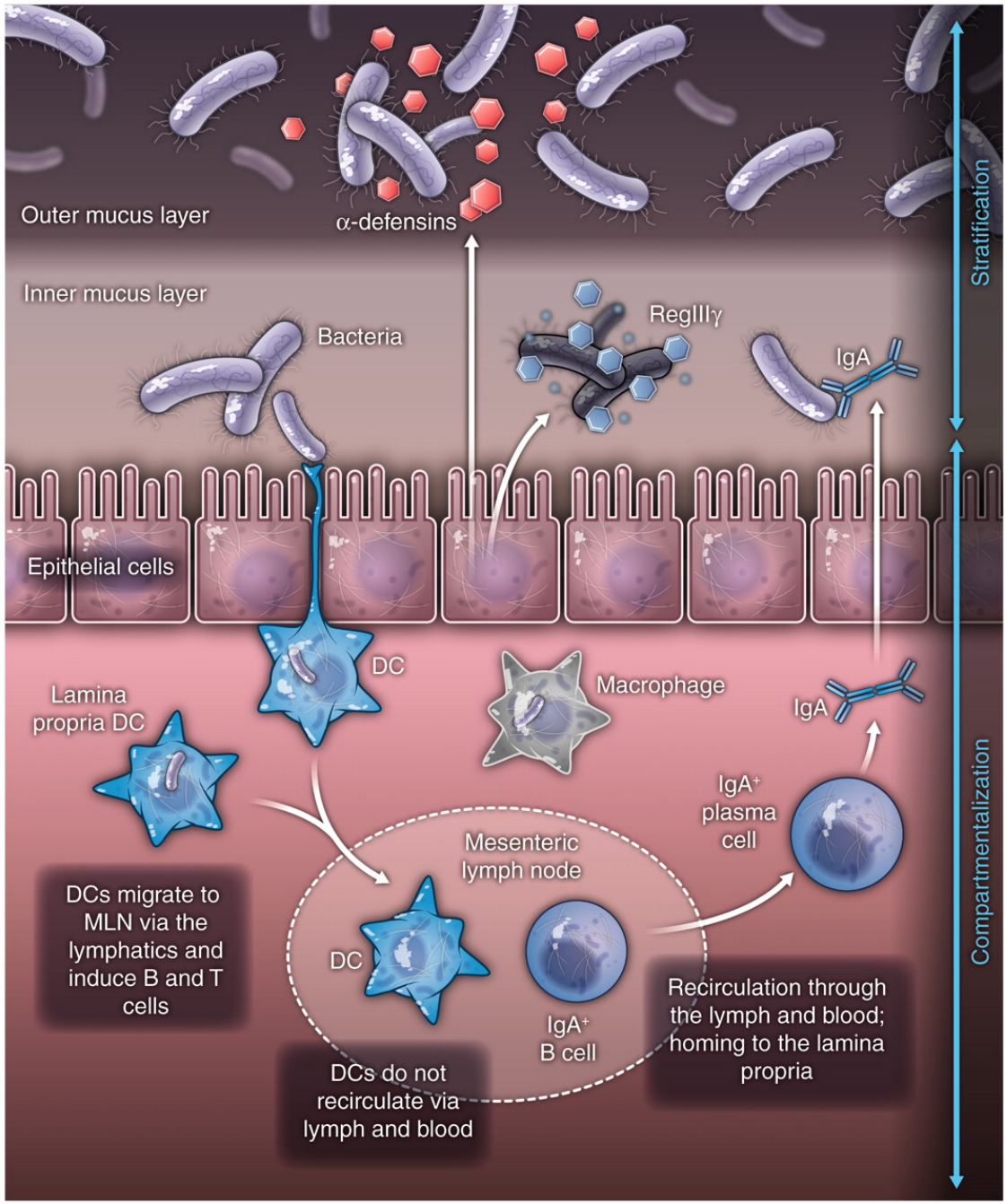
Nature 486 (2012)

Exploring function through collective databases

National Center for Biotechnology Information

Kegg pathway database

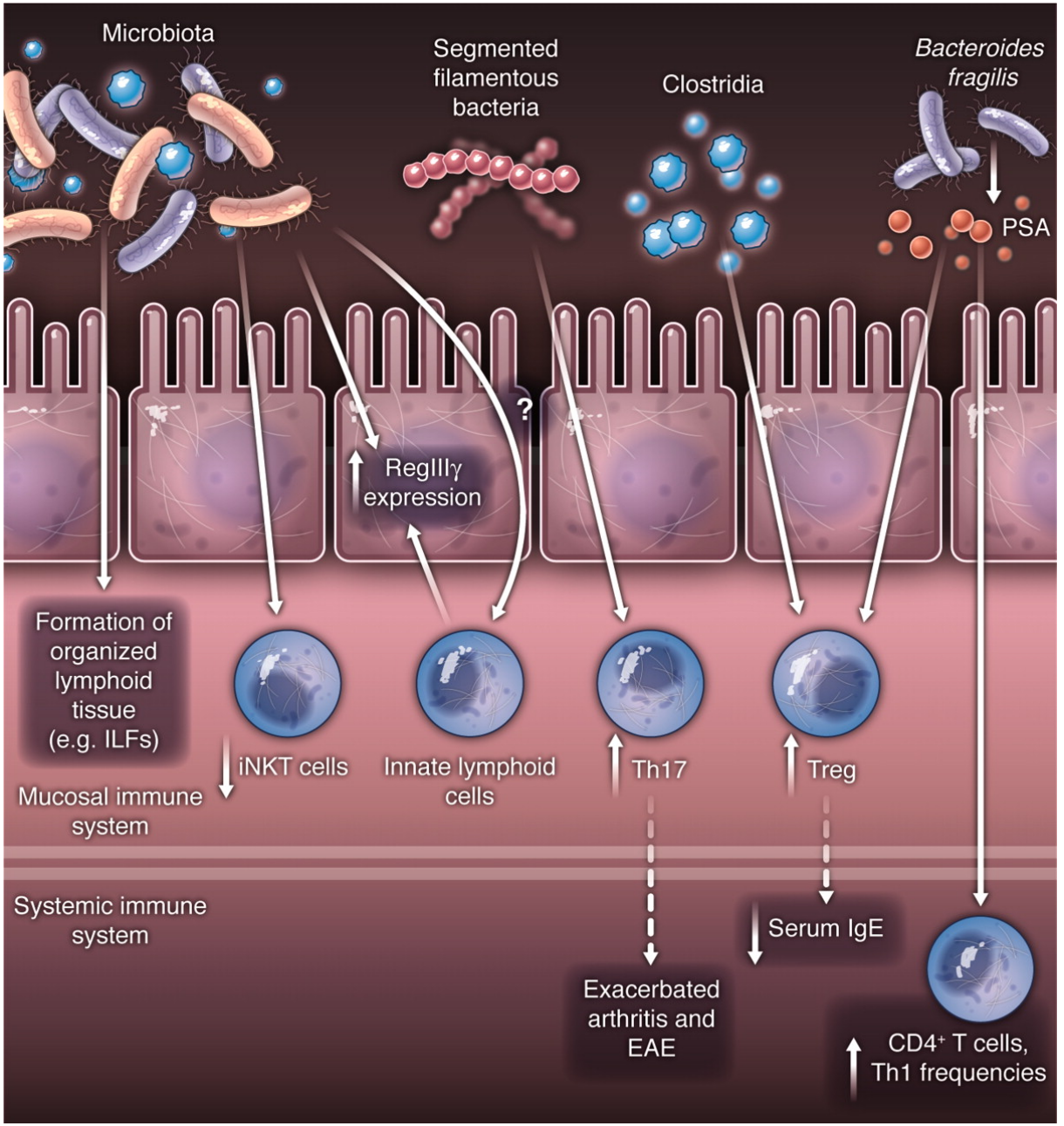
Gut immune effectors function together to stratify luminal microbes and minimize bacterial-epithelial contact



L V Hooper et al. Science 2012;336:1268-1273

Gut microbes shape host immune development in many ways

- Early colonization events are important
- Effects lymphoid structure/development
- Effects intestinal epithelial function
- Microbiota shape T cell subsets
- Effects on systemic immunity - Can protect against autoimmune disease



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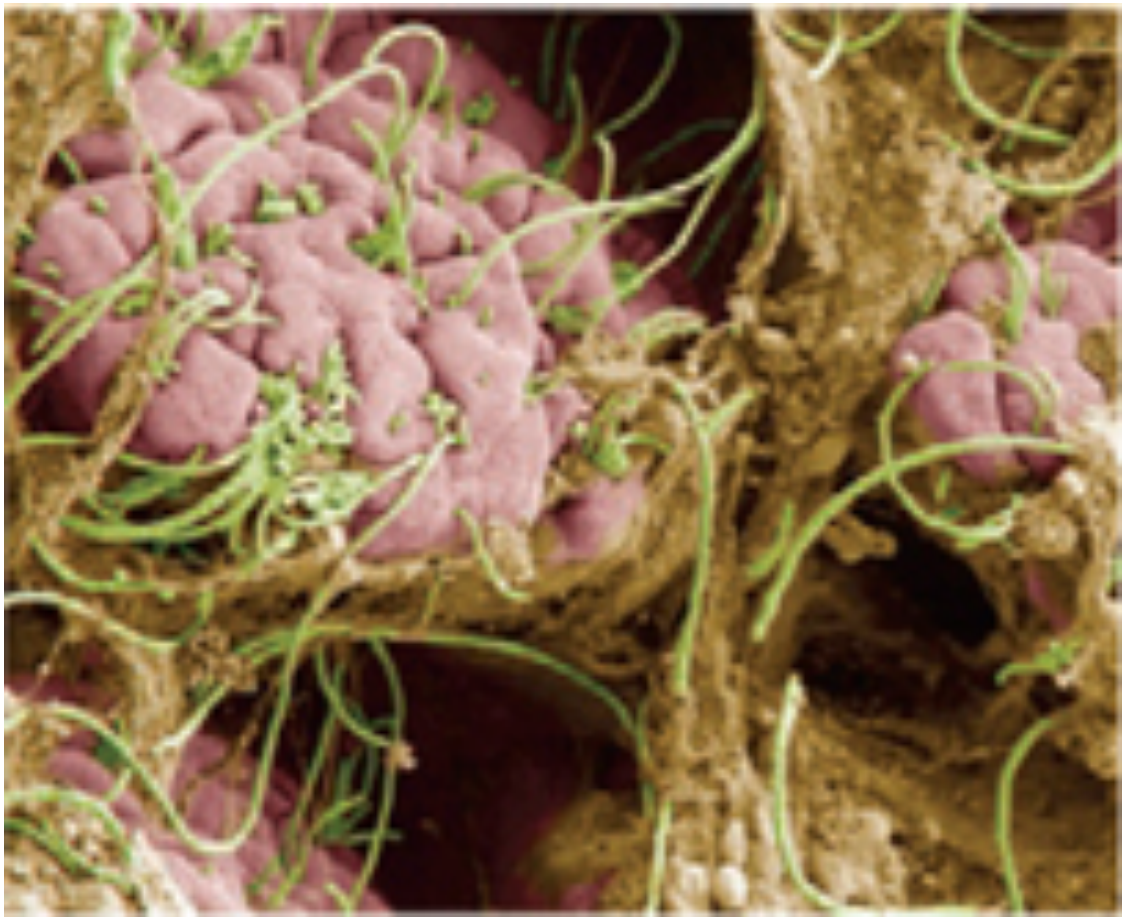
Are there species that might do the opposite?



Prime for response?

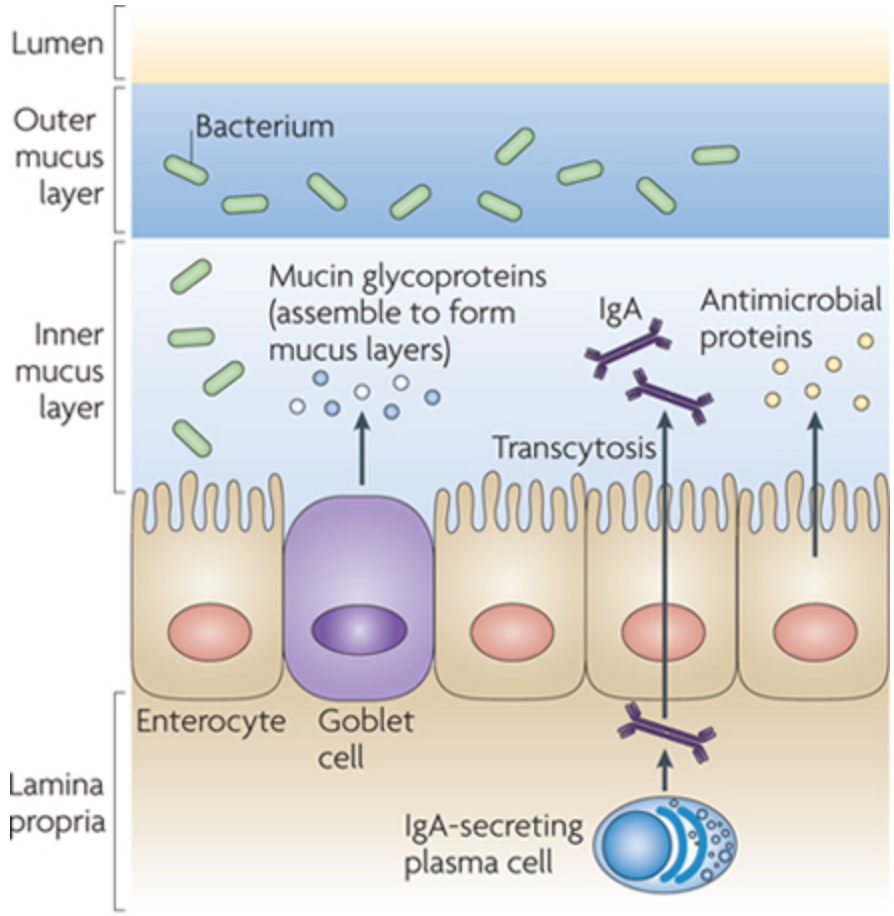
Sequence analysis

UniFrac

1) Alpha and beta diversity

2) Qualitative or quantitative ?
unweighted or weighted

3) Phylogeny or taxon based



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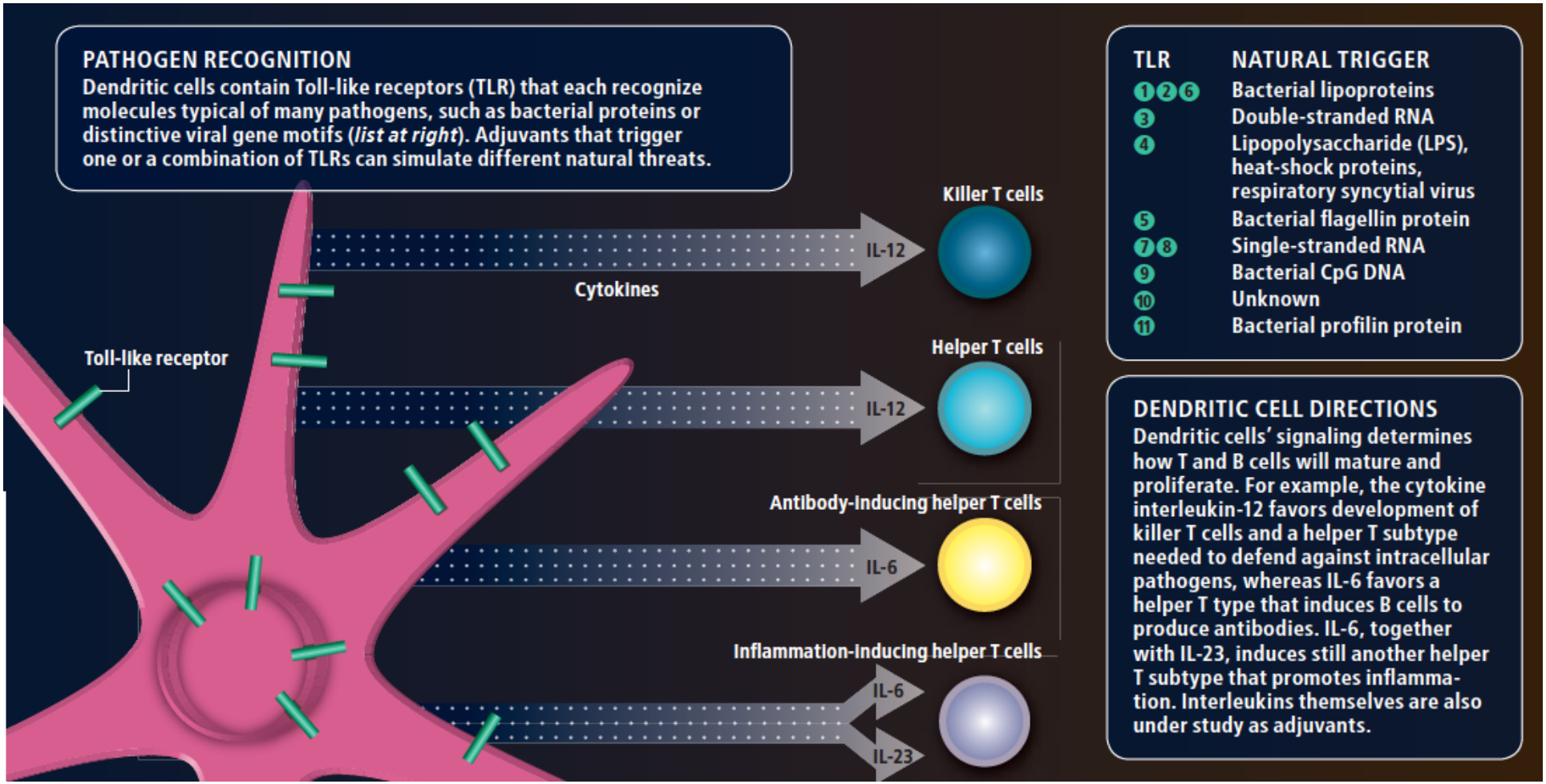
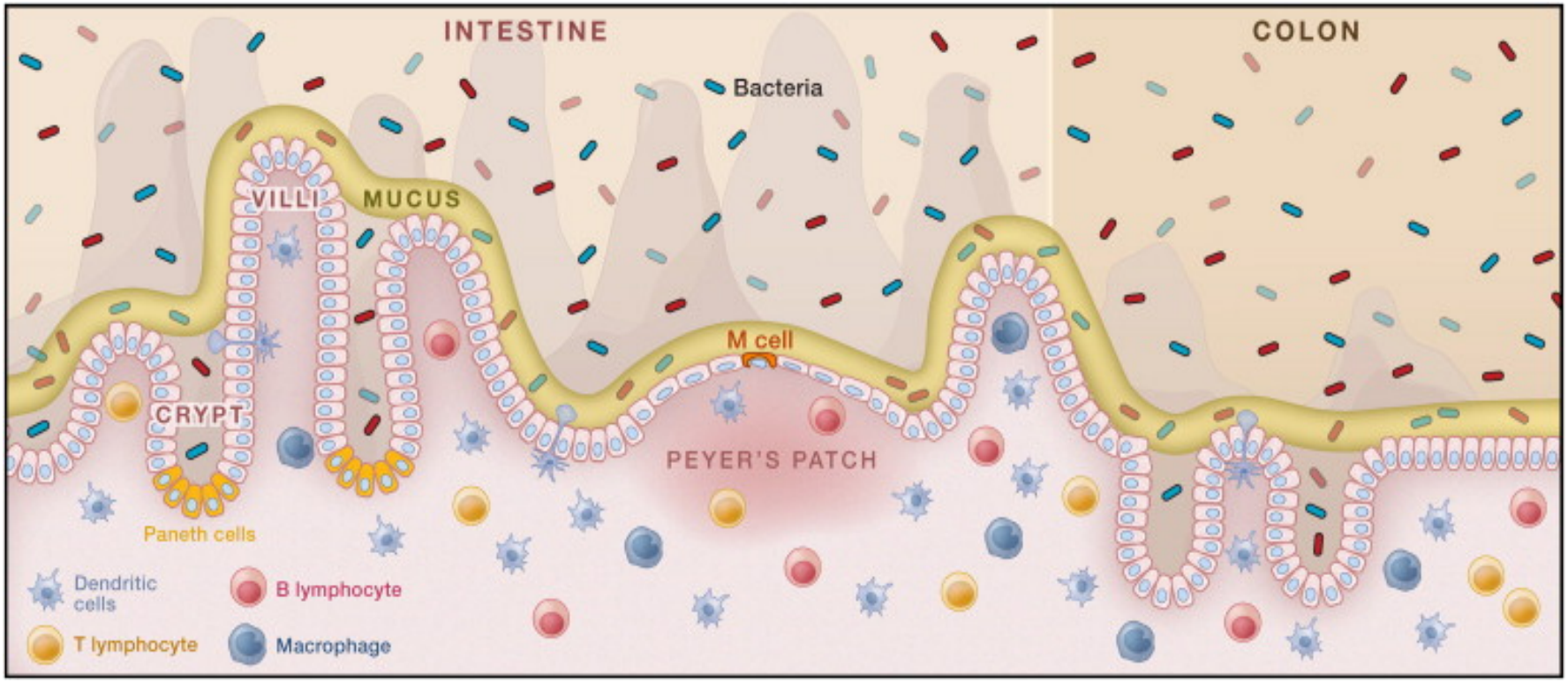
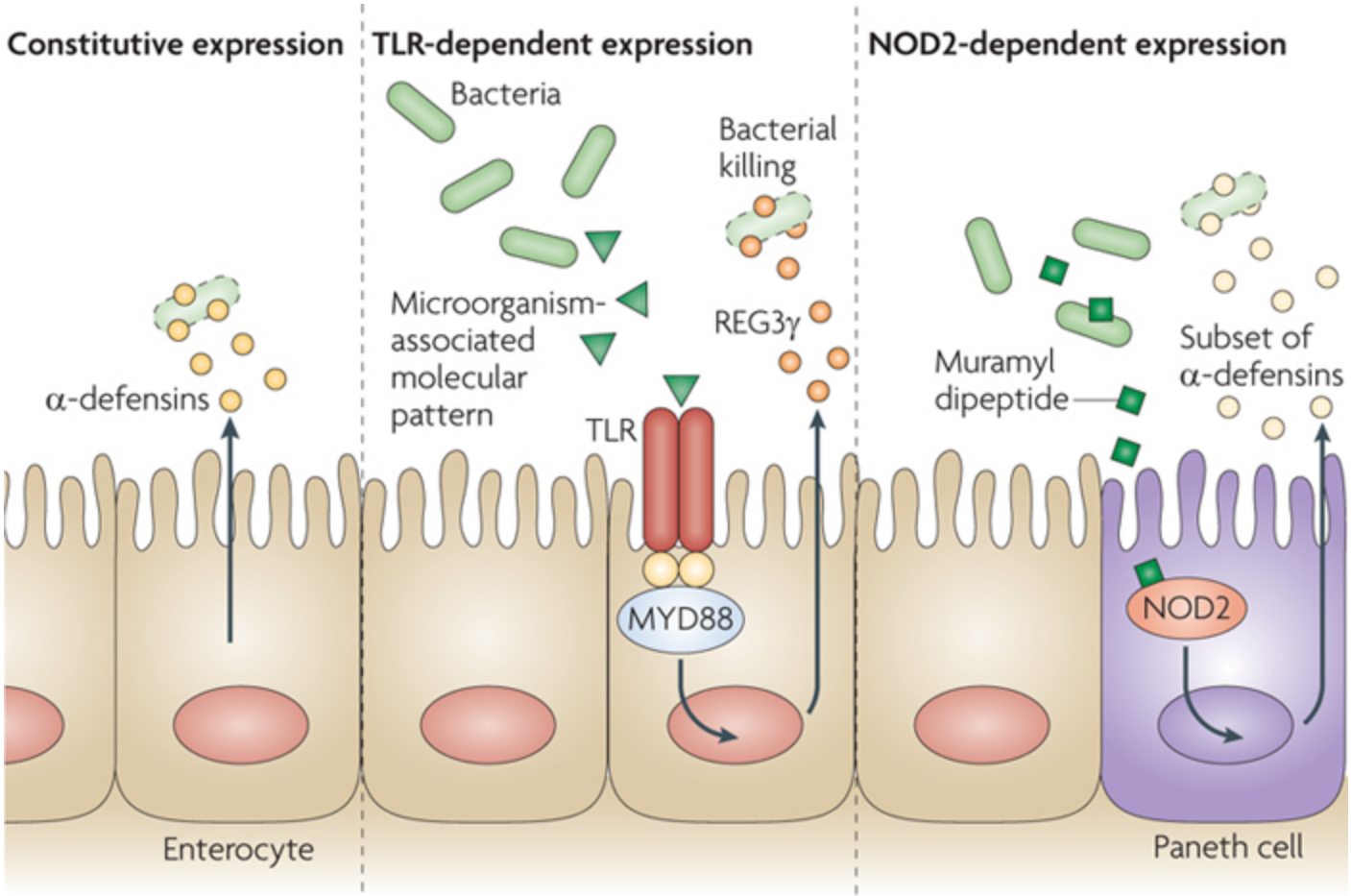

PATHOGEN RECOGNITION
Dendritic cells contain Toll-like receptors (TLR) that each recognize molecules typical of many pathogens, such as bacterial proteins or distinctive viral gene motifs (*list at right*). Adjuvants that trigger one or a combination of TLRs can simulate different natural threats.
Toll-like receptor
Cytokines
IL-12
Killer T cells
IL-12
Helper T cells
IL-6
Antibody-inducing helper T cells
IL-6
IL-23
Inflammation-inducing helper T cells
TLR
NATURAL TRIGGER
1 2 6 Bacterial lipoproteins
3 Double-stranded RNA
4 Lipopolysaccharide (LPS), heat-shock proteins, respiratory syncytial virus
5 Bacterial flagellin protein
7 8 Single-stranded RNA
9 Bacterial CpG DNA
10 Unknown
11 Bacterial profilin protein
DENDRITIC CELL DIRECTIONS
Dendritic cells' signaling determines how T and B cells will mature and proliferate. For example, the cytokine interleukin-12 favors development of killer T cells and a helper T subtype needed to defend against intracellular pathogens, whereas IL-6 favors a helper T type that induces B cells to produce antibodies. IL-6, together with IL-23, induces still another helper T subtype that promotes inflammation. Interleukins themselves are also under study as adjuvants.

Immunological defect	Site	Phenotype in germ-free mice compared with conventionally housed mice
Development of small intestine	Peyer's patches	Fewer and less cellular
	Lamina propria	Thinner and less cellular
	Germinal centres	Fewer plasma cells
	Isolated lymphoid follicles	Smaller and less cellular
Development of mesenteric lymph nodes	Germinal centres	Smaller, less cellular and with fewer plasma cells
$CD8^+$ T cells	Intestinal epithelial lymphocytes	Fewer cells and with reduced cytotoxicity
$CD4^+$ T cells	Lamina propria	Fewer cells; decreased T_H17 cells in the small intestine but increased T_H17 cells in the colon
$CD4^+CD25^+$ T cells	Mesenteric lymph nodes	Reduced expression of FOXP3 and reduced suppressive capacity
Expression of angiogenin 4	Paneth cells	Reduced
Expression of REG3γ	Paneth cells	Reduced
Production of secretory IgA	B cells	Reduced
Levels of ATP	Intestine	Reduced
Expression of MHC class II molecules	Intestinal epithelial cells	Reduced
Expression of TLR9	Intestinal epithelial cells	Reduced
Levels of IL-25	Intestinal epithelial cells	Reduced

FOXP3, forkhead box P3; IL-25, interleukin 25; REG3γ; regenerating islet-derived 3γ; T_H17, T helper 17; TLR9, Toll-like receptor 9.



Cell Volume 140, Issue 6 2010 859 - 870



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