

# The role of microbiota in pathogenesis of inflammatory and neoplastic diseases. Contribution of germ-free models of human diseases

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# Microbiome analysis

The DNA sequencing revolution brought human genome analysis (2000) and later (2010) human microbiome analysis - „human second genome“. Using advanced molecular-biological methods (metagenomics) it was possible to analyse the composition of microbiota present on various epithelial body surfaces.

## Projects:

Metagenomics of the Human Intestinal Tract - MetaHIT“ (EC)  
Human Microbiome Project - HMP (USA NIH)

New „multi-omics“ approaches are used to analyze the functions of microbiota

- transcriptomics - gene expression
- proteomics - protein production
- metabolomics - metabolites production
  
- Gnotobiology - physiological and pathological effects of colonization of germfree animals

# **Gnotobiology-establishment and rearing of gnotobiotic animals without microbiota („germ-free“-GF) or animals colonized with defined microbiota**

**Gnotobiology: from greek „gnotos“- known, „bios“- life  
Gnotobiological laboratory of the Institute of Microbiology  
in Nový Hrádek established in early sixties  
by prof. Jaroslav Šterzl, MD, DSc.**



**Jaroslav Šterzl (1925-2012)**



**Rearing of germfree mice in plastic isolators  
Sterile delivery, sterile air, water and food**

# **Gnotobiotic animal models - tool to study the microbiota involvement in immunity development and in etiopathogenesis of human diseases**

**It was shown that microbiota:**

- Exert profound effect on physiological and immunological development**
- Participate in pathogenic mechanisms of chronic inflammatory and autoimmune diseases**
- Are involved in carcinogenesis and affect tumor therapy**
- Open the possibility of novel preventive and therapeutic approaches by modulation of mucosal ecosystem**

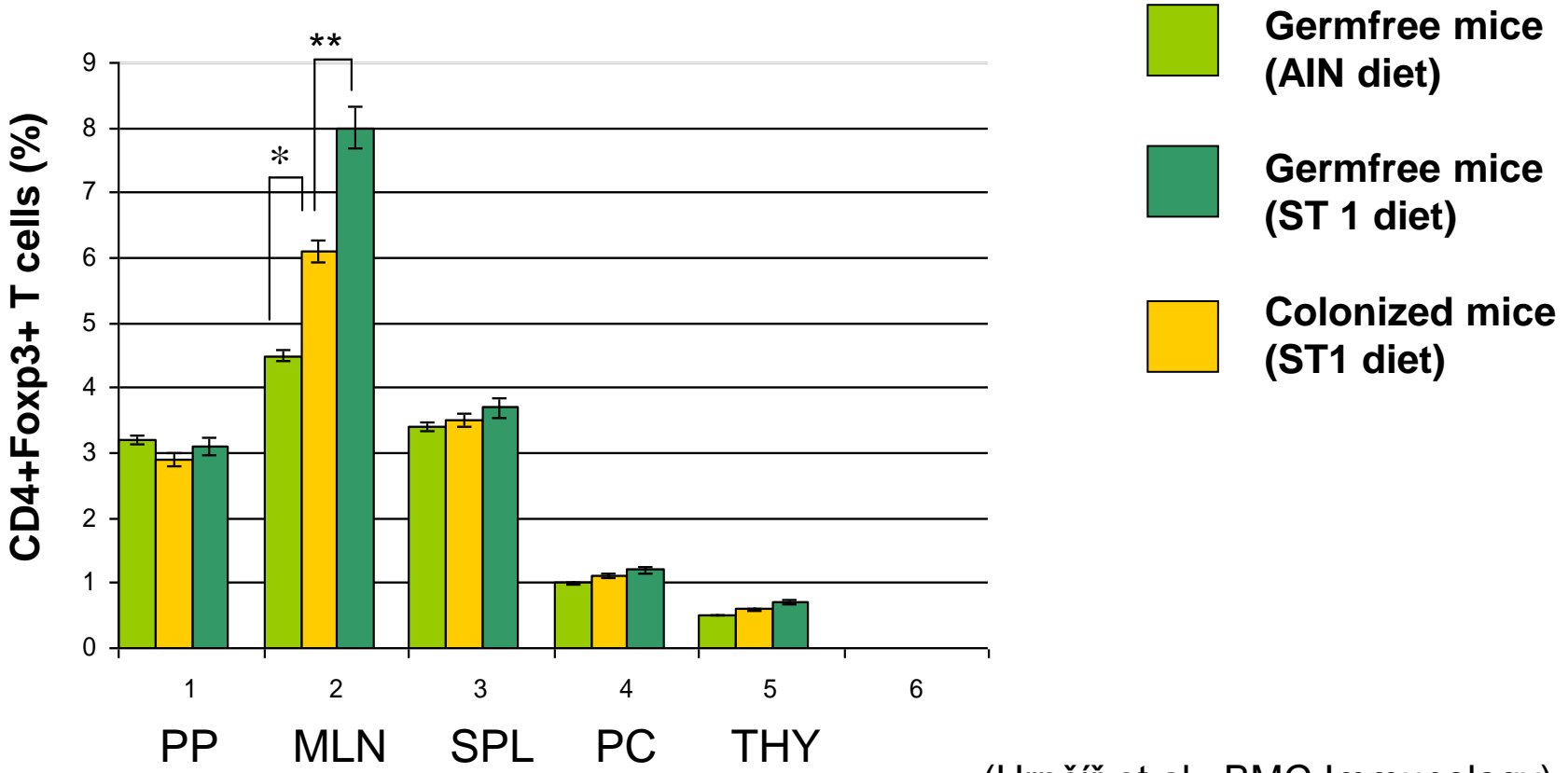
**Mouse models of human diseases used in our laboratories to analyse the role of microbiota:**

**Inflammatory bowel disease (IBD), colorectal carcinoma, atherosclerosis, type I diabetes, psoriasis, uveitis, allergy, ankylosing enthesopathy**

# The effect of microbiota and orally applied lipopolysaccharide on mucosal immunity development



## Colonization of GF mice with microbiota or feeding with LPS containing diet induced expansion of CD4+Foxp3+ T regulatory cells in mesenteric lymph nodes (FACS)



(Hrnčíř et al., BMC Immunology)

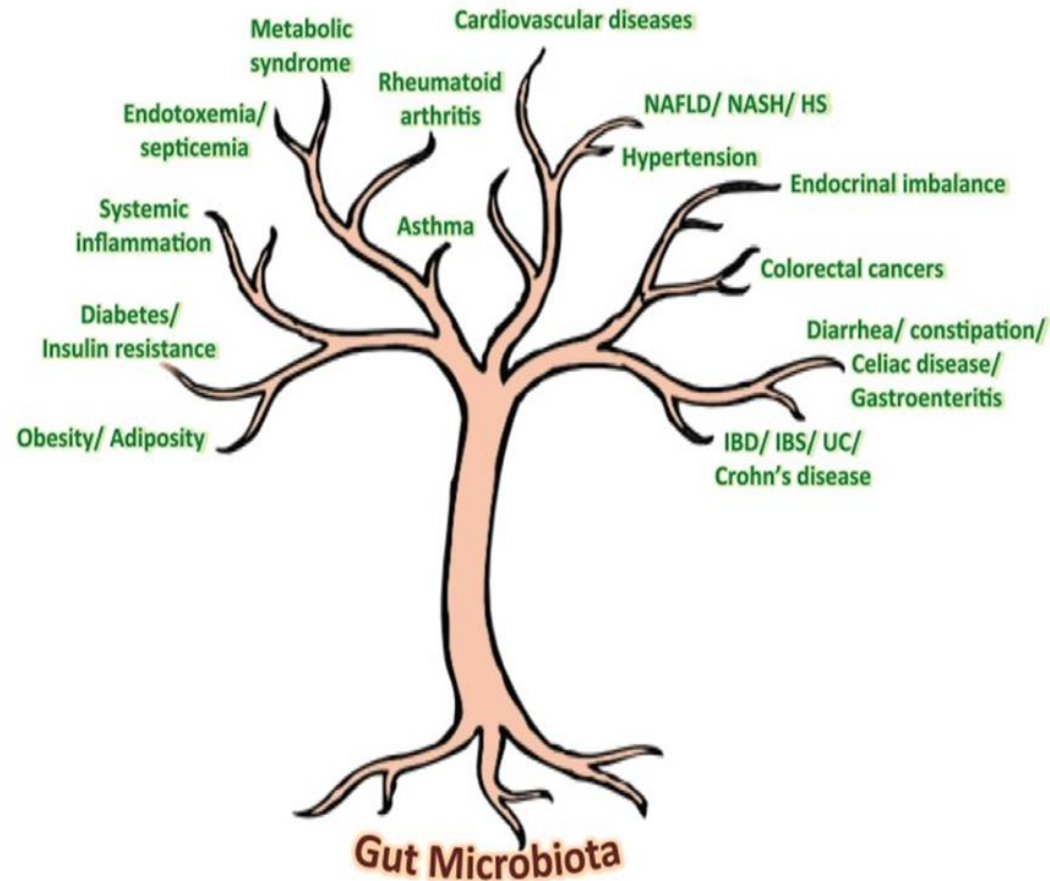
# The role of microbiota in chronic diseases

Many chronic diseases are associated with dysbiosis (microbial dysbalance)

## Dysbiosis:

deviated repertoire of intestinal microbiota:

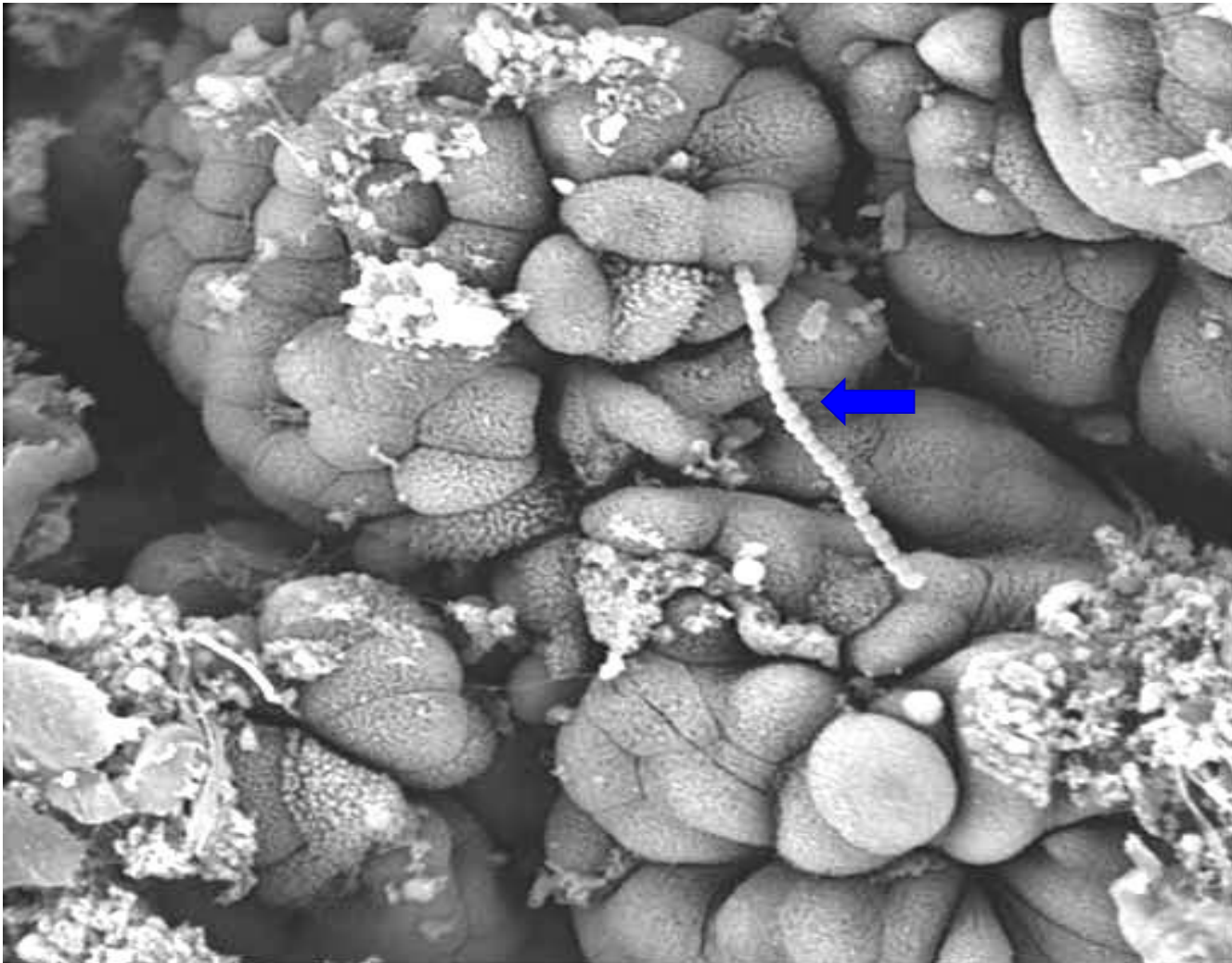
- decreased diversity,
- increase of pathobionts
- decreased beneficial microbes



**Cause or association ???**

# Experimental gnotobiotic model of human Crohn disease

Colonization of germ-free mice with bacterial cocktail containing segmented filamentous bacteria (SFB) leads to severe intestinal inflammation



**SFB**

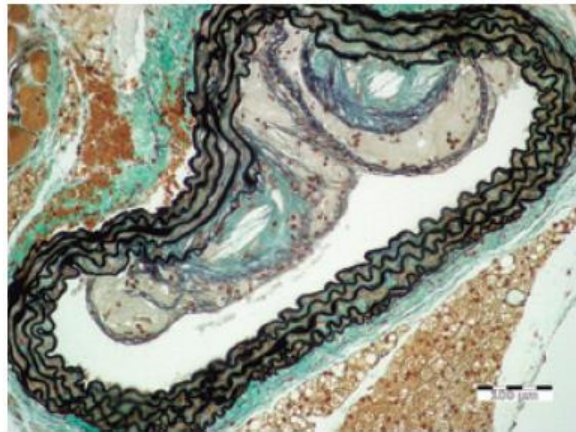
(Štěpánková et al., Inflammatory Bowel Disease)

# Experimental model of human atherosclerosis



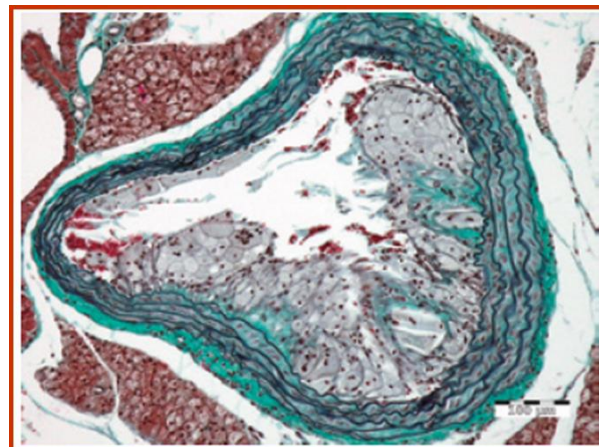
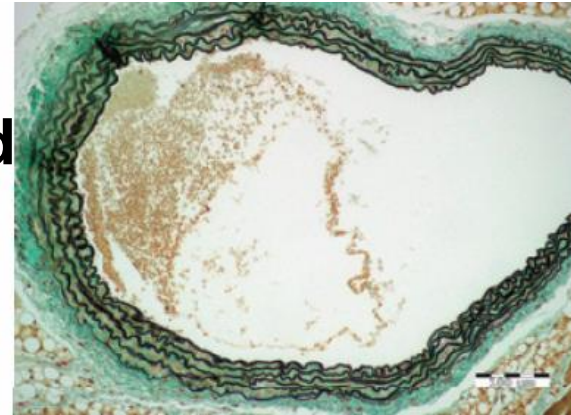
## Protective effect of commensal bacteria on atherosclerosis development in ApoE<sup>-/-</sup> mice fed standard diet

**Germ-free**

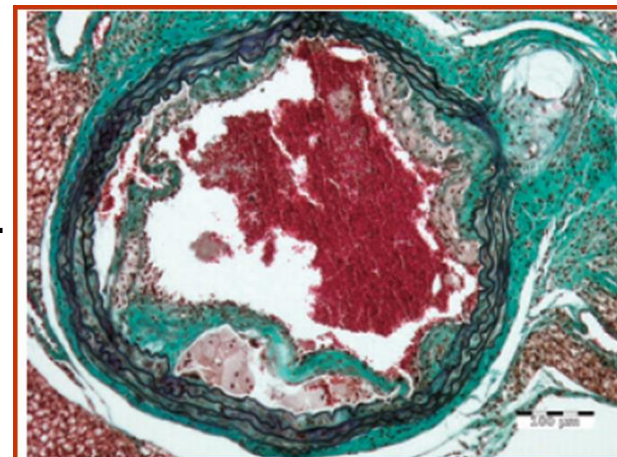


**Standard diet**

**Colonized**



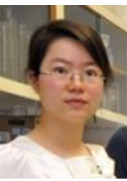
**High cholest. diet**



(Štěpánková et al., J. Ather. Thromb. 2010)



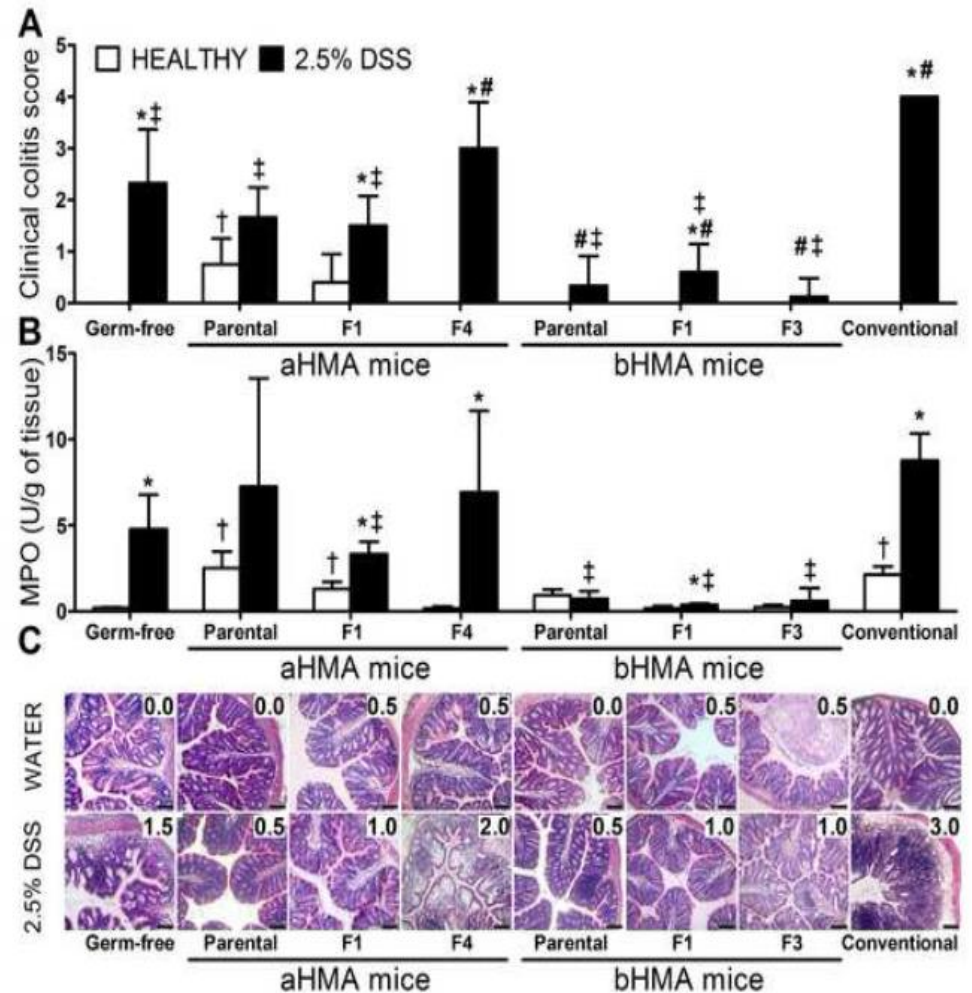
# „Humanized“ mice



Transfer of mucosa associated microbiota from intestinal biopsy of patients with ulcerative colitis into germ-free mice allows to analyse inflammatory potential of IBD microbiota

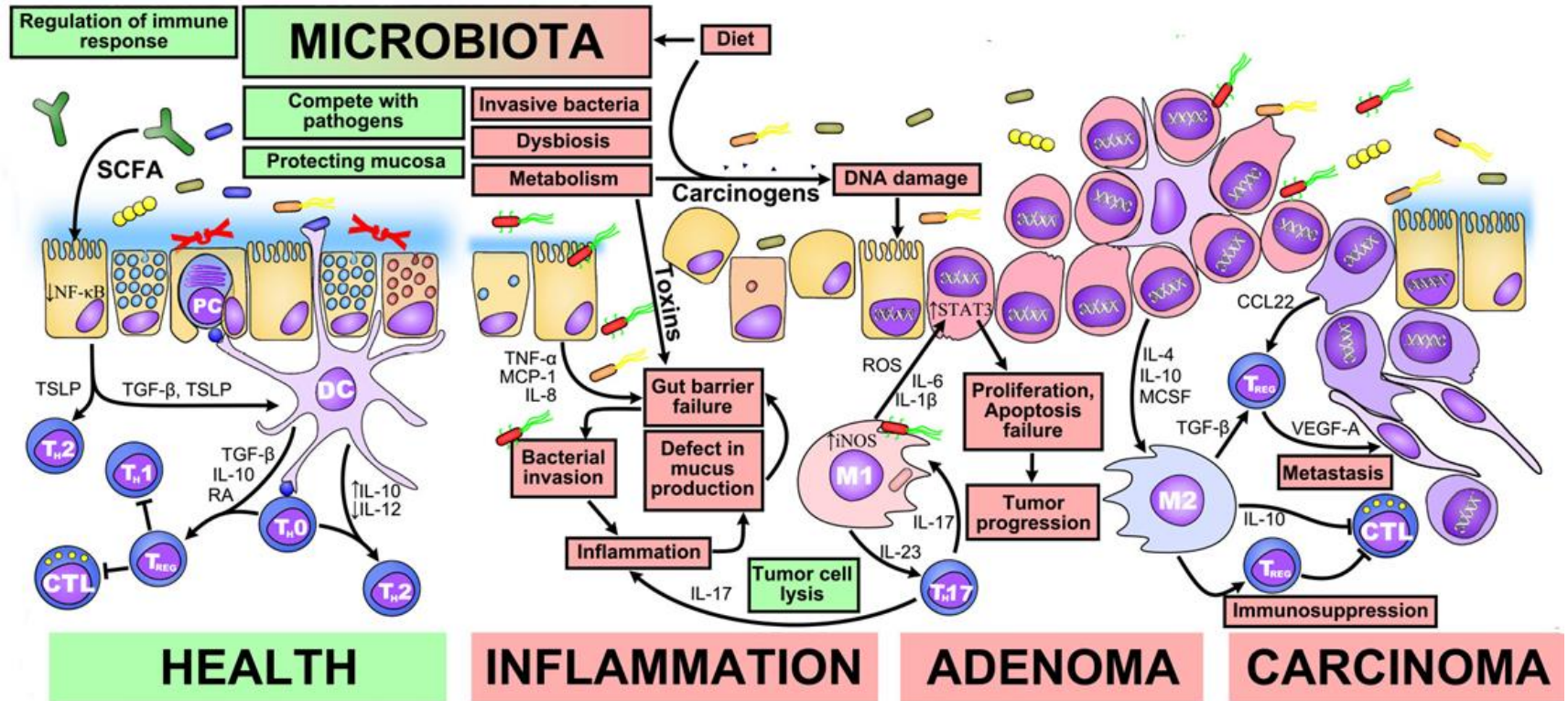
Macro- and microscopic evaluation of colitis

(Zhengyu Du, et al., Gut Pathogens 2016)



# Alteration of immunological balance during inflammation and carcinogenesis

(Tlaskalová-Hogenová et al. Cancer J.2014)



# Conclusions

- **The common finding of dysbiotic microbiota in patients with chronic non transmissible diseases suggests the involvement of microbiota in etiopathogenesis of these disorders. However the proof of causal relationship is still missing!**
- **Gnotobiotic models of human diseases are helping to elucidate the role of microbes and their components in development of diseases. Modulation of mucosal (gut) and skin ecosystems using these animal models represent important tool to find and define health- promoting microbial species or products and to translate successful regimens into clinical therapies.**
- **Microbiota-targeted and microbial- based therapies (eg. diet, prebiotics, probiotics, live biotherapeutic products, bacteriophages, fecal microbiota transfer) applied in personalized regimens thus represent promising approaches for prevention and treatment of these diseases.**

***Institute of Microbiology, Academy of Sciences of the Czech Republic,  
Prague and Nový Hrádek, Czech Republic***

# *Acknowledgement*



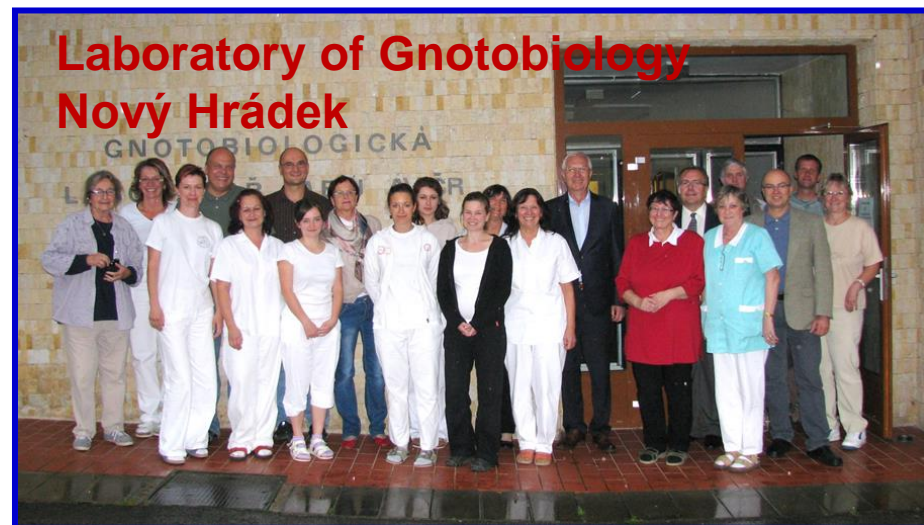
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*Graphic Design: Veronika Patrovská*



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