Dangerous liaisons between gene and microbiota: the example of Card9 in IBD

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ProbiHote
Genes in IBD

Crohn’s Disease
140 risk loci

Ulcerative colitis
133 risk loci

Identified in GWAS

30

110

23

Card9

Khor et al. Nature 2011
Jostins et al. Nature 2012
Card9: a central adaptor molecule in innate immunity

NFkB/P38/JNK
Th1/Th17 polarization

ROS (oxydative burst)

NFkB
pro-IL1b
Card9 KO mice are more susceptible to DSS-induced colitis.

Colon transcriptomics

WT
Card9-/-

DSS

Sokol et al. Gastroenterology 2013
Card9 KO mice are more susceptible to DSS-induced colitis

Reg3γ and Reg3β down regulated in Card9−/− mice

Card9 KO mice are more susceptible to DSS-induced colitis

Colon transcriptomics

WT
Card9-/-

**
**

Days
Weight (%)

DSS
Colon transcriptomics

IL-22, RegIIIγ, RegIIIβ: involved in response to microorganisms

⇒ Effects on gut microbiota?

Card9 KO mice have an altered bacterial and fungal microbiota

Does the dysbiotic microbiota play a role in inflammation by itself?

*Lamas et al. Nature Medicine 2016*
Role of the microbiota in Card9 KO-mice susceptibility to inflammation

Bruno Lamas
The microbiota from $\textit{Card}9^{-/-}$ mice exerts proinflammatory effects

\textit{Lamas et al. Nature Medicine 2016}
The IL22 pathway is impaired $\text{Card}9^{-/-} \rightarrow \text{GF mice}$
Transfer of the IL22 defect through microbiota hypothesis = impaired function of the microbiota

TRYPTOPHAN

Host Cells (IDO1)

Kynurenine

Microbiota

Indole derivates (IAA)

AhR

+ +

IL-22
Card9⁻/⁻ → GF mice exhibits impaired tryptophan metabolism

Kynurenin → IDO → Kynurenine → Indole derivates (IAA)
Card9\(^{-/-}\) mice exhibits impaired tryptophan metabolism.
Card9\(^{-/-}\) mice exhibits impaired tryptophan metabolism

TRYPTOPHAN

Card9\(^{-/-}\)

Microbiota

Indoles derivates (IAA)

AhR

IL-22

Colitis
Card$9^{-/-}$ mice exhibits impaired tryptophan metabolism

Can we rescue the phenotype with AhR agonists?
AhR agonist rescue the phenotype in Card9⁻/⁻ → GF mice

AhR ligand-producing bacteria rescue the phenotype in Card9\(^{-/-}\) \rightarrow GF mice

![AhR activity graph]

**Culture supernatant (20%)**

<table>
<thead>
<tr>
<th>AhR activity (Fold change)</th>
<th>WT</th>
<th>Card9(^{-/-})</th>
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</thead>
<tbody>
<tr>
<td><strong>Culture Media</strong></td>
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<tr>
<td>L. murinus CNCM I-5020</td>
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<tr>
<td>L. reuteri CNCM I-5022</td>
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<tr>
<td>L. taiwanensis CNCM I-5019</td>
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</tbody>
</table>

**Culture supernatant**

- **2%**
- **10%**
- **20%**

**Gavage with WT mice feces**

- GF WT
- D0
- D7
- D14
- D21
- DSS 2%
- H\(_2\)O
- AhR antagonist or vehicle
- Gavage with Bacteria or vehicle
AhR ligand-producing bacteria rescue the phenotype in Card9−/− → GF mice

AhR ligand-producing bacteria rescue the phenotype in Card9−/− → GF mice

**Weight (%)**

Days after initial DSS exposure

**AhR activity**

Fold changes

**IL-22**

Relative expression

pg/mg of colon

Relevance in Human?

AhR activity (Fold changes)

HS
IBD

***

Tryptophan (nmol/g)

HS
IBD

***

Kynurenine (nmol/g)

HS
IBD

***

IAA (nmol/g)

HS
IBD

***

IBD: n = 112
HS: n = 37

Relevance in Human?

Card9 SNP associated with IBD

rs10781499

A h R activity (Fold change)

Nod2_score

ATG16L1_rs12994997

LRRK2_rs11564258

Conclusion

• Gut microbiota has a central role in IBD pathogenesis
• It is under the influence of both environmental and genetic factors
Conclusion

- Gut microbiota in IBD pathogenesis: chicken or egg?

Both!
Sokol’s lab

Collaborators
HL Pham  ILTOO Pharma
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JM Launay  Unit 970 Inserm
RJ Xavier  Broad /Harvard / MGH

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