Serum IgG Response to the Hinge Peptide of Flagellin Predicts Future Crohn's Disease Onset

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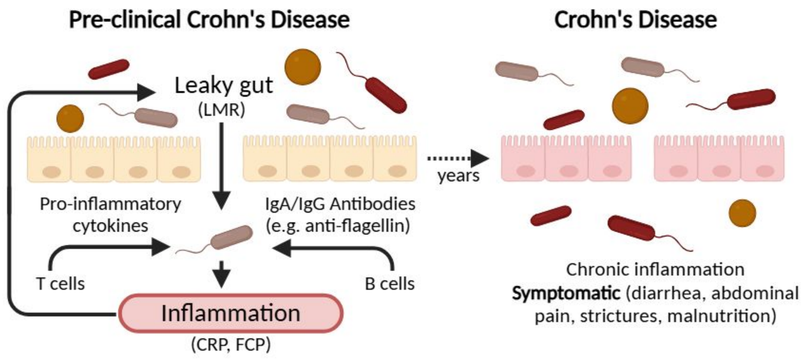
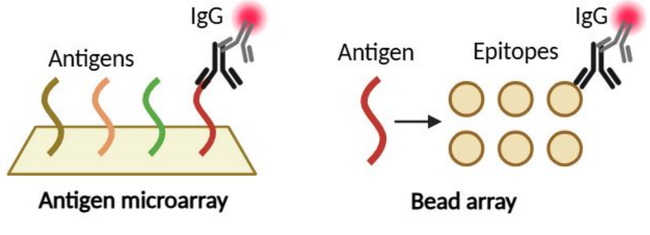
Introduction

- **Crohn's disease (CD)**: Chronic inflammatory bowel disease involving a loss of tolerance to commensal gut bacteria
  - Associated with **elevated antibody responses** against microbial antigens
  - Lack of understanding of early immune dysregulation in pre-Crohn's disease (pre-CD)
- **Objective**: Characterize pre-CD antibody responses to microbial antigens



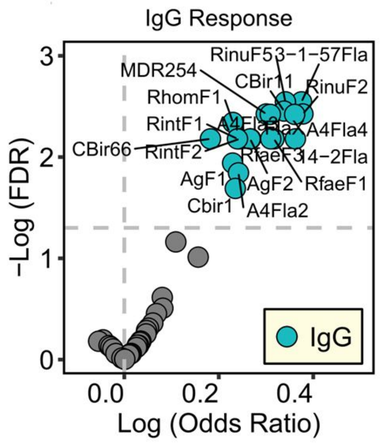
Methods

- **Cohort**: Healthy first-degree relatives of CD patients in the CCC-GEM study, including pre-CD cases (n=77) and matched controls (n=304)
  - Also measured baseline CRP, FCP, LMR
- **Antibody Analysis**:
  - Antigen microarray to identify reactivity against against a broad spectrum of **antigens**
  - Bead array to identify reactivity against **epitopes** of a certain antigen (i.e. flagellin)



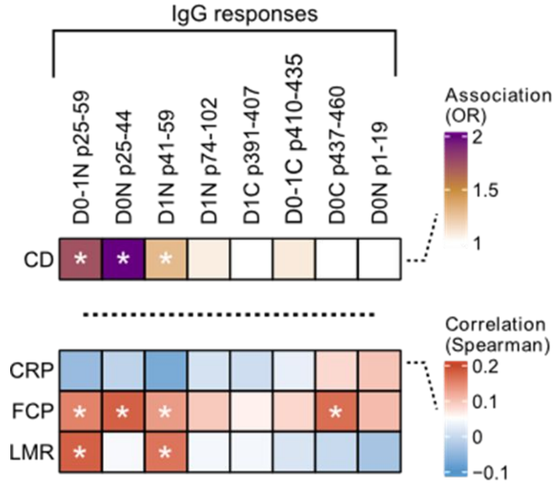
Results: Antigen Microarray

- 19 IgG antibody responses were associated with future CD onset
- All 19 IgGs targeted **flagellins** (proteins that compose the flagella) from the *Lachnospiraceae* family



Results: Flagellin Bead Array

- Focussed the analysis to examining seroreactivity to 8 epitopes of *Lachnospiraceae* flagellin
- IgG response to **hinge region** epitopes (D0N p25-44, D1N p41-59, D0-1N p25-59) were associated with future CD onset and also FCP (inflammatory marker) and LMR (leaky gut)



Discussion

- Early IgG antibody responses to *Lachnospiraceae* flagellins, particularly to the hinge peptide, may reflect immune activation before CD onset
  - Anti-flagellin responses may also contribute to barrier dysfunction and early inflammation in pre-CD
- Aligns with previous studies linking anti-flagellin antibodies with severe CD phenotypes and complications (e.g. stricture, surgery rates)
  - Our study further shows that the anti-flagellin antibody response are already present well before CD diagnosis

Strengths:

- Focus on pre-disease state
- Large cohort and matched controls

Limitations:

- Lack of mechanistic experiments

Conclusion

- Pre-CD patients exhibit distinct IgG responses to *Lachnospiraceae* flagellins, driven by a conserved hinge peptide
- These findings highlight potential for anti-flagellin antibody responses as biomarkers for early CD detection and insights into CD pathophysiology
  - Hinge peptide may be an early immune target in pre-CD

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Presented by Sean Jeong

Evidence of Conflict of Financial Interest

	Co-author	**Conflict disclosures**
1	Sean Jeong	No conflicts to disclose
2	Richard Wu	No conflicts to disclose
3	Mingyue Xue	No conflicts to disclose
4	Williams Turpin	No conflicts to disclose
5	Sun-Ho Lee	No conflicts to disclose
6	Kenneth Croitoru	No conflicts to disclose

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