Increased Expression of LRRK2, a Susceptibility Gene of IBD Results in Enhanced Pro-Inflammatory Response and Severe Experimental Colitis

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Disclosure

Patent: Janssen Pharmaceuticals:
The use of anti-IL-12p40 mAb for the treatment of Crohn’s disease patients

LRRK2/MUC19 Locus has the Second Strongest Association with IBD in GWAS Studies

Crohn’s disease  Ulnceative colitis  Total IBD
Gene       Odds Ratio  Gene       Odds Ratio  Gene       Odds Ratio
1. IL23R    2.271      1. IL23R    1.662      1. IL23R    2.013
2. Nod2      1.557      2. HLA region 1.444      2. LRRK2/MUC19 1.334
3. LRRK2/MUC19 1.463  3. IL-10     1.277      3. Nod2      1.295
4. IRGM      1.324      4. IRGM      1.249
5. PTGER4    1.294      5. TAB1      1.209
6. TAB1      1.247
7. ATG16L1   1.233      17. LRRK2/MUC19 1.163

Jostins L et al. 2012 Nature
Many SNPs are associated with LRRK2 gene region

• rs11564258 is located downstream of LRRK2 gene and intron1 of MUC19 gene

Franke et al., 2010 J Hum Genet

LRRK2 Transgenic Mice Exhibit Severe Experimental Colitis

Methods
• Lrrk2 transgenic mice (Lrrk2 Tg)
• 2% Dextran Sodium Sulfate (DSS)-induces colitis

Results
• Lrrk2 Tg mice show more severe colitis compared to Wt littermate controls.

Only Zymosan Stimulation Induces Significant Increases in Cytokines by LRRK2 Tg Mice

Methods
• Bone marrow-derived dendritic cells (BMDC)
• in vitro Stimulation with TLR ligands
• ELISA

Results
• LPS (TLR4), PGN and FSL-1 (TLR2) stimulation didn’t show significant difference
• Zymosan which can stimulate Dectin-1 and TLR2 shows significant increase in Lrrk2 Tg
**LRRK2 Positively Regulates Dectin-1, an innate immune receptor of β-glucans**

**Methods**
- BMDC in vitro Stimulation with Dectin-1 ligands: Zymosan depleted (ZymD), Heat-killed S. Cerevisiae (HK-SC), Heat-killed Candida albicans (HK-CA).
- ELISA

**Results**
- Dectin-1 agonists induced increased response in Lrk2 Tg.

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**LRRK2 Interacts with TAK1 Complex**

**Methods**
- HEK293T cells were transfected with LRRK2 and TAK1, TRAF6, NEMO or TAB2 vector.
- Immunoprecipitation and Western Blotting

**Results**
- LRRK2 binds to TAK1, TRAF6, NEMO and TAB2.

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**LRRK2 Activates NF-KB and MAP Kinase Signaling upon Dectin-1 Stimulation**

**Methods**
- BMDC
- in vitro Stimulation with ZymD
- Western Blotting

**Results**
- BMDC from Lrk2 Tg show increased NF-kB and MAP kinase in response to ZymD.

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LRRK2 Causes Decreased Autophagy through Inhibition of Beclin-1

LRRK2 Inhibition Results in Amelioration of Inflammation

Summary

- Lrrk2 Tg mice display increased severity of colitis.
- LRRK2 thru Dectin-1 signaling interacts with TAK1 complex and activates NF-κB signaling.
- LRRK2 can bind and inactivate Beclin-1 resulting in decreased Autophagy.
- Inhibitors of LRRK2 can ameliorate experimental inflammation.
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