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Reactive oxygen species generated by NADPH oxidase-1 and Dual oxidase-2 contribute to inflammatory bowel disease

Statement of the Problem: Gut microbes play an essential role in pathogenesis of inflammatory bowel disease (IBD). Host cells respond to microbe colonization by releasing cytokines and chemokines. Some inflammatory cytokines such as IL-4 and IL-13 induce NADPH oxidase-1 (NOX1) and dual oxidase-2 (DUOX2) gene expression in the epithelial cells. Elevated NOX1 or DUOX2 can produce reactive oxygen species (ROS) to regulate various cellular functions including cell proliferation, migration and apoptosis. NOX1 and DUOX2 have been linked to very-early-onset IBD, beginning before 6 years old. But the exact role of NOX1 and DUOX2 in IBD is not known.

Methodology: Mice deficient in antioxidant enzymes, glutathione peroxidase (GPx)-1 and -2, so called GPx1/2-DKO mice, develop ileocolitis around weaning. The hall-mark of pathology includes high crypt apoptosis, Paneth cell depletion, exfoliation and crypt abscess. Germ-free DKO mice are disease-free. To explore the role of Nox1 and Duox2 in gut inflammation, we studied the pathology and phenotype of Nox1-GPx1/2-triple KO (TKO) and Duox-GPx1/2-TKO mice at 35 days of age (comparable to human very-early-onset IBD).

Findings: Nox1-Gpx1/2-TKO mice virtually do not have pathology. Duox-GPx1/2-TKO mice have intermediate pathology except crypt apoptosis remain as high as the DKO mice.

Conclusions & Significance: Both Nox1 and Duox2 contribute to inflammation, while Nox1 has a stronger impact than Duox2 probably because it is expressed in the crypt of the gland. Drugs that have been effective in treating IBD, such as dexamethasone and antibiotics, are likely mediated through suppression of NOX1 and DUOX2 gene expression.

Recent Publications

1. Chu F F et al. (2004) Bacteria-induced intestinal cancer in mice deficient in both Gpx1 and Gpx2 genes. Cancer Res. 64:962-968.
2. Hayes P et al. (2015) Defects in HADPH oxidase genes NOX1 and DUOX2 in very early onset inflammatory bowel disease. Cell Mol. Gastroenterol. Hepatol. 1(5):489-502.
3. Chu F F et al. (2017) Deficiency in Duox2 activity alleviates ileitis in GPx1- and GPx2-knockout mice without affecting apoptosis incidence in the crypt epithelium. Redox Biology. 11:144-156.
4. Liu H et al. (2017) Interleukin-4 and interleukin-13 increase NADPH oxidase 1-related proliferation of human colon cancer cells. Oncotarget. 8(24):38113-38135.

Biography

Fong Fong Chu has her expertise in gastrointestinal diseases especially in inflammatory bowel disease (IBD). Her team has established a mouse model of IBD which is very-early onset. These mice are deficient in two isoenzymes which reduce hydrogen peroxide named GPx1/2-double knockout (DKO). This model is a better model than chemical-induced colitis models because it is not injury based and mimic closely to human IBD. She has built this model through 20 years of research and has identified new targets for IBD therapy. She joined Beckman Research Institute of the City of Hope, Duarte CA USA (1987). She is currently associated with the Department of Gastroenterology & Hepatology and the First Affiliated Hospital and College of Clinical Medicine of Henan University of Science and Technology, Luoyang, Henan, P R China since 2016.

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