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The immunoregulation effect of dendritic cells GITRL on asthma with early life lipopolysaccharide pre-exposure

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Background: Asthma is one of the most common chronic respiratory diseases in children. Lipopolysaccharide(LPS) is found in the cell wall of Gram-negative bacteria and is a ubiquitous component in our environment. Studies showed that LPS enhanced antigen-specific allergic responses, while other studies showed that LPS exposure protected from asthma. Our previous study found that the discrepancies may be due to the different LPS exposure concentrations and stages, and low-dose LPS inhalation in neonatal mice induces endotoxin tolerance, thereby offering protection from later asthma development by increasing Treg cells while decreasing Th2 and Th17 cells. It's reported that the ligand of glucocorticoid-induced tumour necrosis factor receptor (GITRL) plays an important role in immunoregulation by inhibiting Treg cells while inducing CD4+T cells. However, its role in modulating allergic asthma is unknown.

Methods: Three-day-old wild-type and Toll-like receptor 4 (TLR4)-deficient neonatal mice were exposed to low-dose LPS (1ug) intranasally for 10 consecutive days prior to ovalbumin (OVA)-induced asthma. Primary CD11c+DCs and CD4+T-cells with or without low-dose LPS pre-exposure before OVA stimulation were co-cultured in vitro. The T cells skewing and DCs GITRL were measured. Meanwhile, asthma phenotype is measured after artificial GITRL over-expression, to confirm the effect of GITRL in asthma mice with low-dose LPS pre-exposure.

Results: Low-dose LPS pre-exposure upregulated the Treg response and downregulated pathogenic Th2 and Th17 responses through promoting apoptosis of Th2 and Th17 cells. Low-dose LPS pre-exposure downregulated dendritic cells (DCs) GITRL expression and T-cell GITR expression. Artificial DCs GITRL expression abrogated

the tolerogenic Treg-skewing effect of low-dose LPS pre-exposure. Low-dose LPS pre- exposure inhibited TRIF/IRF3/IFNβ signaling in a TLR4- dependent manner and this tolerogenic DCs GITRL downregulation was attributable to TRIF/IRF3/IFNβ signaling inhibition.

Conclusions: Low-dose LPS pre-exposure produces tolerogenic Treg skewing in neonatal asthmatic mice, a phenomenon attributable to TLR4-dependent TRIF/IRF3/IFNβ-mediated DCs GITRL downregulation.

Recent Publication

1. Liu, Bo et al. "Human umbilical cord mesenchymal stem cell conditioned medium attenuates renal fibrosis by reducing inflammation and epithelial-to-mesenchymal transition via the TLR4/NF-κB signalling pathway in vivo and in vitro." Stem cell research & therapy vol. 9,1 7. 12 Jan. 2018, doi:10.1186/s13287-017-0760-6

2. Liu, Bo et al. "Human umbilical cord-derived mesenchymal stem cells conditioned medium attenuate interstitial fibrosis and stimulate the repair of tubular epithelial cells in an irreversible model of unilateral ureteral obstruction." Nephrology (Carlton, Vic.) vol. 23,8 (2018): 728-736. doi:10.1111/nep.13099

3. Liu, Bo et al. "Risk of venous and arterial thromboembolic events associated with VEGFR-TKIs: a meta-analysis." Cancer Chemotherapy and Pharmacology vol. 80,3 (2017): 487-495. doi:10.1007/s00280-017-3386-6

Biography

Fengxia Ding is a respiratory medicine physician and pediatrician from Children's Hospital of Children's Hospital of Chongqing Medical University & Chongqing Medical University, one of the top three children's hospital in China. Now she is working as a post doctor in Great Ormond Street Institute of Child Health, University College London (UCL). She has been working as a pediatrician for 7 years in Children's Hospital of Children's Hospital of Chongqing Medical University & Chongqing Medical University, and there are more than 19,000 outpatient pediatric patients visit she every year. She got a patent in respiratory diseases, and she has over 30 publications focusing on respiratory disease and asthma. She has presented her clinical and research work at many conferences and got many grands on her researchers.

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