Methods and Compositions for Treating Inflammatory Diseases

Tech ID: 33049 / UC Case 2019-199-0

BACKGROUND

Immune responses are crucial in fighting against infections. An uncontrolled immune response, however, can be deadly. Sepsis is one such inflammatory disease that can lead to organ failure and death, so it is crucial to develop new sepsis therapies. Long noncoding RNAs (lncRNAs), although not translated into proteins themselves, can regulate gene expression in biological processes. Studies have shown that lncRNAs can regulate immune responses, which leads to substantial interest in implicating lncRNAs in inflammatory diseases.

TECHNOLOGY DESCRIPTION

This invention involves inhibitors of gastric adenocarcinoma predictive long intergenic noncoding (GAPLINC) RNA, a type of lncRNA, and is based on UC Santa Cruz researchers' discovery that GAPLINC plays a role in regulating inflammation. GAPLINC knockdown studies suggested that GAPLINC negatively regulates the inflammatory response. Depleting GAPLINC increased expression of immune response genes. Furthermore, in response to endotoxic shock, *Gaplinc* knockout mice showed 100% survival, whereas wild type mice showed 0% survival after 2 days. By inhibiting GAPLINC, treatment for sepsis can start to go beyond supportive care.

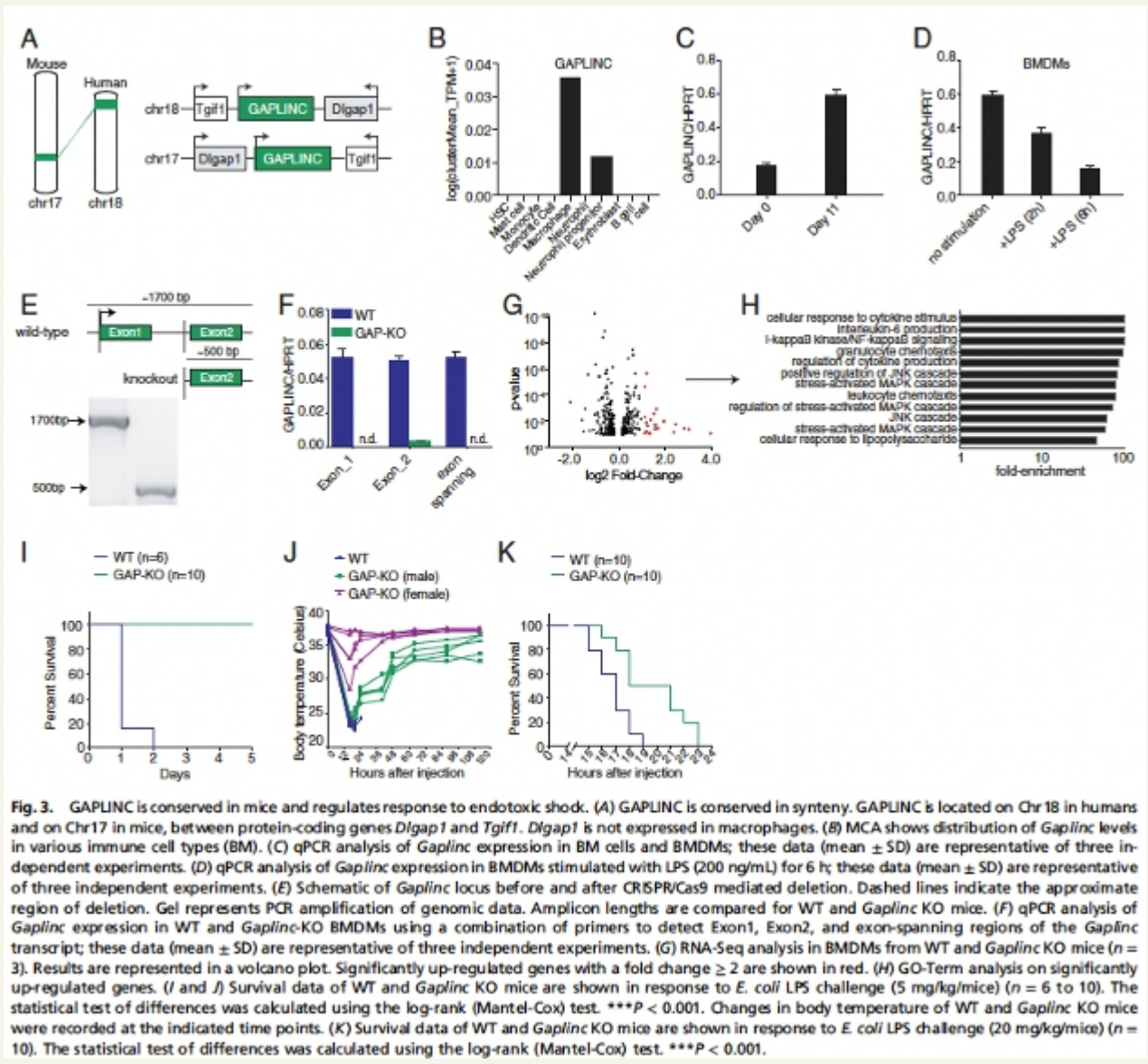


Fig. 3. GAPLINC is conserved in mice and regulates response to endotoxic shock. (*A*) GAPLINC is conserved in synteny. GAPLINC is located on Chr 18 in humans and on Chr17 in mice, between protein-coding genes *Dlgap1* and *Tgif1*. *Dlgap1* is not expressed in macrophages. (*B*) MCA shows distribution of *Gaplinc* levels in various immune cell types (BM). (*C*) qPCR analysis of *Gaplinc* expression in BM cells and BMDMs; these data (mean ± SD) are representative of three independent experiments. (*D*) qPCR analysis of *Gaplinc* expression in BMDMs stimulated with LPS (200 ng/mL) for 6 h; these data (mean ± SD) are representative of three independent experiments. (*E*) Schematic of *Gaplinc* locus before and after CRISPR/Cas9 mediated deletion. Dashed lines indicate the approximate region of deletion. Gel represents PCR amplification of genomic data. Amplicon lengths are compared for WT and *Gaplinc* KO mice. (*F*) qPCR analysis of *Gaplinc* expression in WT and *Gaplinc*-KO BMDMs using a combination of primers to detect Exon1, Exon2, and exon-spanning regions of the *Gaplinc* transcript; these data (mean ± SD) are representative of three independent experiments. (*G*) RNA-Seq analysis in BMDMs from WT and *Gaplinc* KO mice (n = 3). Results are represented in a volcano plot. Significantly up-regulated genes with a fold change ≥ 2 are shown in red. (*H*) GO-Term analysis on significantly up-regulated genes. (*I* and *J*) Survival data of WT and *Gaplinc* KO mice are shown in response to *E. coli* LPS challenge (5 mg/kg/mice) (n = 6 to 10). The statistical test of differences was calculated using the log-rank (Mantel-Cox) test. ***$P < 0.001$. Changes in body temperature of WT and *Gaplinc* KO mice were recorded at the indicated time points. (*K*) Survival data of WT and *Gaplinc* KO mice are shown in response to *E. coli* LPS challenge (20 mg/kg/mice) (n = 10). The statistical test of differences was calculated using the log-rank (Mantel-Cox) test. ***$P < 0.001$.

APPLICATIONS

CONTACT

Jeff M. Jackson
jjackso6@ucsc.edu
tel: .



INVENTORS

- Carpenter, Susan
- Covarrubias, Sergio
- Vollmers, Apple

OTHER INFORMATION

KEYWORDS

long noncoding RNA, inflammation, GAPLINC, innate immunity, sepsis, p65

CATEGORIZED AS

- **Medical**
  - Disease: Autoimmune and Inflammation
  - Therapeutics

RELATED CASES

2019-199-0

- therapeutic intervention
- sepsis treatment
- RNA therapeutics
- novel drug development

ADVANTAGES

- unmet need

INTELLECTUAL PROPERTY INFORMATION

Country	Type	Number	Dated	Case
United States Of America	Published Application	20210087563	03/25/2021	2019-199

RELATED MATERIALS

- A conserved long noncoding RNA, GAPLINC, modulates the immune response during endotoxic shock - 02/10/2021

ADDITIONAL TECHNOLOGIES BY THESE INVENTORS

- Hek293 Cell Line Producing Murine GM-CSF
- CRISPRware

University of California, Santa Cruz
Industry Alliances & Technology Commercialization
Kerr 413 / IATC,
Santa Cruz,CA 95064

Tel: 831.459.5415
innovation@ucsc.edu
https://officeofresearch.ucsc.edu/
Fax: 831.459.1658

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