

DESIGNAÇÃO DO PROJETO

Circadian regulation of innate lymphoid cells

CODIGO DO PROJETO

LISBOA-01-0145-FEDER-028366
PTDC/MED-IMU/28366/2017

REGIÃO DA INTERVENÇÃO

Grande Lisboa

ENTIDADES BENEFICIÁRIAS

FUNDAÇÃO D. ANNA DE SOMMER CHAMPALIMAUD E DR. CARLOS MONTEZ CHAMPALIMAUD

DATA DE APROVAÇÃO

13/03/2018

DATA DE INÍCIO

14/06/2018

DATA DE CONCLUSÃO

13/06/2022

CUSTO TOTAL ELEGÍVEL

224.917,71€

APOIO FINANCEIRO DA
UNIÃO EUROPEIA (FEDER)

89.967,08€

APOIO FINANCEIRO
PÚBLICO NAC. (OE)

134. 950,63€

OBJETIVOS, ATIVIDADES E RESULTADOS ESPERADOS/ATINGIDOS

Objectives:

We proposed to elucidate the role of the circadian clock in ILC3 by deciphering:

1. Role of the circadian clock in ILC3 homeostasis
2. Circadian control of ILC3 function in health and disease
3. Environmental cues entraining the ILC3-autonomous circadian clocks

Results:

- In this project we have been exploring the role of circadian cues in ILC biology. Notably, we found light-entrained and brain-tuned circadian circuits regulate enteric ILC3, intestinal homeostasis, gut defence and the host lipid metabolism (Godinho-Silva et al. Nature 2019).

- We have shown that light-entrained and brain-tuned circadian circuits regulate enteric ILC3, intestinal homeostasis, gut defence and the host lipid metabolism. We found that enteric ILC3 displays circadian expression of clock genes and ILC3-related transcription factors. ILC3-autonomous ablation of the circadian regulator Arntl leads to disrupted gut ILC3 homeostasis, impaired epithelial reactivity, deregulated microbiome, increased susceptibility to bowel infection and disrupted lipid metabolism. Loss of ILC3-intrinsic Arntl shapes the gut postcode receptors of ILC3. Strikingly, light-dark cycles, feeding rhythms and microbial cues differentially regulate ILC3 clocks, with light signals as major entraining cues of ILC3. Accordingly, surgical- and genetically-induced deregulation of brain rhythmicity leads to disrupted circadian ILC3 oscillations, deregulated microbiome and altered lipid metabolism. Our work revealed a circadian circuitry that translates environmental light cues into enteric ILC3, shaping intestinal health, metabolism and organismal homeostasis. This cornerstone study was published in Nature in 2019 (Godinho-Silva et al. Nature 2019).

- In parallel, we have been exploring how circadian cues regulate type 2 ILC biology. To this end, we have been employing state-of-the-art genetics to generate an accurate genetic mouse model. Thus, we generated Arntl conditional knockout mice by breeding Arntl floxed mice to Il7ra-Cre and Il5-Cre mice. These animals are currently being analyzed. Excitingly, our data indicate that circadian cues critically regulate type 2 innate responses.

Activities:

- 8 articles publicatations in international scientific journals with scientific refereeing;
- Oral Communications: 30; "Communications-Poster": 3;
- PhD thesis: 2
- Patent: 2