

※ 考生請注意：本試題不可使用計算機。請於答案卷(卡)作答，於本試題紙上作答者，不予計分。

1. Please read the abstract and answer the following questions:

Bile acids are abundant in the mammalian gut, where they undergo bacteria-mediated transformation to generate a large pool of bioactive molecules. Although bile acids are known to affect host metabolism, cancer progression and innate immunity, it is unknown whether they affect adaptive immune cells such as T helper cells that express IL-17a (TH17 cells) or regulatory T cells (Treg cells). Here we screen a library of bile acid metabolites and identify two distinct derivatives of lithocholic acid (LCA), 3-oxoLCA and isoalloLCA, as T cell regulators in mice. 3-OxoLCA inhibited the differentiation of TH17 cells by directly binding to the key transcription factor retinoid-related orphan receptor- $\gamma$ t (ROR $\gamma$ t) and isoalloLCA increased the differentiation of Treg cells through the production of mitochondrial reactive oxygen species (mitoROS), which led to increased expression of FOXP3. The isoalloLCA-mediated enhancement of Treg cell differentiation required an intronic Foxp3 enhancer, the conserved noncoding sequence (CNS) 3; this represents a mode of action distinct from that of previously identified metabolites that increase Treg cell differentiation, which require CNS1. The administration of 3-oxoLCA and isoalloLCA to mice reduced TH17 cell differentiation and increased Treg cell differentiation, respectively, in the intestinal lamina propria. Our data suggest mechanisms through which bile acid metabolites control host immune responses, by directly modulating the balance of TH17 and Treg cells. (*Nature*. 2019 Dec;576(7785):143-148.)

a. Please briefly describe what you know about TH17 cells and Treg cells. (10%)

b. Please briefly describe key transcription factors responsible for differentiation of TH1, TH2, TH17 and Treg cells. (8%)

c. Please briefly describe what you know about intestinal lamina propria. (7%)

d. Please briefly discuss the distinctive features of mucosal immune system (10 %)

e. In your opinion, what are the contributions of this research? (10%)

2. The Nobel Prize in Physiology or Medicine 2019 was just awarded jointly to William G. Kaelin Jr, Sir Peter J. Ratcliffe and Gregg L. Semenza for their important findings of how cells sense and adapt to oxygen availability.

a. Please briefly describe about this important finding. (10 %)

b. Interestingly, increase of oxygen consumption is important for microbicidal activity of phagocytes. Please discuss what you know about this process. (20 %)

3. What are the potential requirements for development of autoimmune disease? (10%)

4. Please discuss how cancer cells may escape from immunosurveillance. (15%)