(BBSRC DTP) The role of clock dysfunction in obesity-related inflammation and insulin resistance

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Application Deadline: 31 January 2019

Details

Obesity is one of the biggest challenges to public health in the UK and across much of the world. The major threat is in obesity-related metabolic disturbances, which drive insulin resistance, type-2 diabetes, and cardiovascular disease. It is now recognised that defective function of white adipose tissue (WAT) during obesity is directly linked to the severity of metabolic disturbance, and especially the development of insulin resistance. However, it remains unclear what causes adipose tissue dysfunction and how this leads to metabolic disease. We have identified a model in which obesity is not associated by elevated inflammation or loss of insulin sensitivity (Hand 2014). Specifically, mice lacking the circadian clock gene, Rev-erba, develop profound obesity when fed diets high in fat. However, the mice are relatively protected from obesity-related co-morbidities. The circadian clock is already known to play an important role in dictating daily rhythms in both lipid metabolism (Bechtold 2010) and inflammatory response (Gibbs 2014), and may therefore be a key node linking metabolic and inflammatory responses in WAT, and central to obesity-related pathology in this tissue. Immune cell function is acutely sensitive to purterbations of the circadian clock. Our adipose tissue and immune cell profiling at a cellular and molecular level implicates a central role for increased eosinophil response in this protective phenotype. Adipose tissue is an important niche for immune cells namely eosinophils, macrophages, and innate lymphoid cells (ILCs). Eosinophils have been shown to promote glucose tolerance and energy expenditure in the fat and more recently we showed that eoisnophils independent of any other immune cells, mediated a vascular protective effect of perivascular fat. Eosinophils are functionally diverse cells that are able to exert a variety of effects including anti-inflammatory, restorative effects, anti-pathogen and pro-inflammatory roles. Eosinophils contain granules that contain a variety of preformed effector mediators as well as being able to produce proteins de novo. This means they can act instantly or their effector function can be driven by the tissue environment. Eoisnophils have also been shown to interact with other immune cells such as macrophages in the adipose to drive macrophage effector function.

This PhD project will examine how the clock regulates the activity of eosinophils and other innate immune cell populations during obesity, and test directly the role of the clock in mediating inflammatory cell and adipocyte cross-talk. Studies will employ in vivo whole animal physiology, including global and tissue specific transgenics, complimented by single-cell profiling of inflammatory cell linage and activation state.

https://www.research.manchester.ac.uk/portal/david.bechtold.html
https://www.research.manchester.ac.uk/portal/sheena.cruickshank.html
https://www.research.manchester.ac.uk/portal/mudassar.iqbal.html

Entry Requirements:
Applications are invited from UK/EU nationals only. Applicants must have obtained, or be about to obtain, at least an upper second class honours degree (or equivalent) in a relevant subject.

Funding Notes

This project is to be funded under the BBSRC Doctoral Training Programme. If you are interested in this project, please make direct contact with the Principal Supervisor to arrange to discuss the project further as soon as possible. You MUST also submit an online application form - full details on how to apply can be found on the BBSRC DTP website www.manchester.ac.uk/bbsrcdtpstudentships

As an equal opportunities institution we welcome applicants from all sections of the community regardless of gender, ethnicity, disability, sexual orientation and transgender status. All appointments are made on merit.

References

Hand LE, Usan P, Cooper GJS, Xu LY, Ammori B, Aghamohammadzadeh R, Soran H, Greenstein A, Loudon ASI, Bechtold DA, Ray DW (2014) Adiponectin induces A20 expression in adipose tissue to confer metabolic benefit. Diabetes, 2015 Jan;64(1):128-36.

Cunningham PS, Ahern SA, Smith LC, da Silva Santos CS, Wager TT, Bechtold DA. Targeting of the circadian clock via CK1δ/ε to improve glucose homeostasis in obesity. Sci Rep. 2016 ;6:29983.

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