Embryonic stem cell origin of the adipose tissue macrophages

Rendicontazione

Informazioni relative al progetto

ESATM

ID dell'accordo di sovvenzione: 655598

Sito web del progetto

DOI
10.3030/655598

Progetto chiuso

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€ 159 460,80

Coordinato da
UNIVERSITAET ULM
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Questo progetto è apparso in...

Periodic Reporting for period 1 - ESATM (Embryonic stem cell origin of the adipose tissue macrophages)

Periodo di rendicontazione: 2015-10-01 al 2017-09-30

Sintesi del contesto e degli obiettivi generali del progetto

Insulin resistance (IR) is reaching pandemic proportions and it is predicted to emerge as a leading cause of worldwide morbidity by 2030. Immune cells, including the so-called adipose tissue (AT) macrophages (ATMs), have key roles in the development of this disease. Pharmacological intervention to shape ATM differentiation and function holds considerable promise as a therapeutic approach to prevent or combat IR. However, the stem cell origin of ATMs remains unclear, which hinders the development of such prevention or treatment strategies. This project was initiated to define the embryonic origin of ATMs. We have found that a major population of ATMs develops from embryonic hematopoietic stem cells (eHSCs) and not from the bone marrow (BM) as was originally postulated. With the use of lineage tracing and BM chimerism in mouse, and the complementary study of transgenic Xenopus laevis, we confirmed that ATMs develop from eHSCs, and ATM development does not depend on BM hematopoiesis. We have found that ATMs retain self-renewal capacity, which is under hormonal control. We identified neuropeptide FF (NPFF), an appetite-reducing hormone to control homeostatic ATM self-renewal. It is likely that further hormonal regulators exist, which determine ATM self-renewal. Major deliverables of the project have been published in the high-ranked medical journal The Journal of Clinical Investigation 127(7):2842-2854, and in the Journal of Leukocyte Biology 102(3):845-855. Of note, The Journal of Clinical Investigation is a top-tier venue for critical advances in biomedical research and reaches readers across a wide range of medical disciplines, which should aid in the dissemination of our novel results. The mechanisms we have described are novel. In the light of recent findings, the steady-state ATM pool derives from embryonic progenitors, ATM self-renewal and the controlled removal of ATMs by other immune cells. Overall, these mechanisms are likely responsible for the dynamic maintenance of metabolically-healthy ATMs. In obesity, however, these mechanisms are compromised, and monocyte-derived ATMs become prevalent in the AT, which in part accounts for inflammation and IR. The deliverables of this project may open new horizons to prevent IR through self-renewal mechanism of ATMs.

Publications

1. Waqas SFH, Hoang AC, Lin YT, Ampem G, Azegrouz H, Balogh L, Thuróczy J, Chen JC, Gerling IC, Nam S, Lim JS, Martinez-Ibañez J, Real JT, Paschke S, Quillet R, Ayachi S, Simonin F, Schneider EM, Brinkman JA, Lamming DW, Seroogy CM, Röszer T (2017) Neuropeptide FF increases M2 activation and self-renewal of adipose tissue macrophages. The Journal of Clinical Investigation 127(7):2842-2854, corrigendum: 127(9):3559, IF 12.575 doi: 10.1172/JCI90152.

2. Waqas SFH, Noble A, Hoang AC, Ampem G, Popp M, Strauß S, Guille M, Röszer T (2017) Adipose tissue macrophages develop from bone marrow-independent progenitors in Xenopus laevis and mouse. J Leukocyte Biology, 102(3):845-855, IF 4.165 doi: 10.1189/jlb.1A0317-082RR

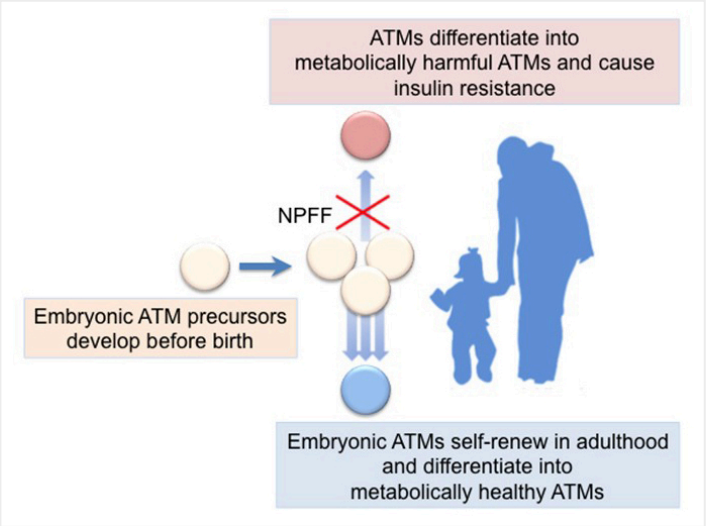
3. Röszer T (2017) Transcriptional control of apoptotic cell clearance by macrophage nuclear receptors. Apoptosis 22(2):284-294., IF 3.592 doi: 10.1007/s10495-016-1310-x.

Lavoro eseguito dall'inizio del progetto fino alla fine del periodo coperto dalla relazione e principali risultati finora ottenuti

This project has addressed the critical question of whether the AT generates ATMs. We raised the hypothesis that AT-associated eHSCs give rise to ATMs, and these ATMs contribute to IR. We could confirm that under homeostatic conditions, ATMs develop from yolk sac progenitors of the macrophage lineage, and ATMs can be replenished without the need for BM hematopoietic progenitors. This proves the core hypothesis, but also refines it: ATMs can be locally generated by ATM self-renewal.

Progressi oltre lo stato dell'arte e potenziale impatto previsto (incluso l'impatto socioeconomico e le implicazioni sociali più ampie del progetto fino ad ora)

Our findings provide a mechanism to explain the origin of ATMs, and complement the model on the steady-state maintenance of the ATM pool. It is a novelty to link the appetite-reducing hormone NPFF to the immune component of obesity and its co-morbidities.



Development of adipose tissue macrophages (ATMs) is key for metabolic health

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Permalink: https://cordis.europa.eu/project/id/655598/reporting/it