## The vascular endothelium of the adipose tissue gives rise to both white and brown fat cells

Andrea Frontini<sup>1</sup>, Khanh-Van Tran<sup>2</sup>, Olga Gealekman<sup>2</sup>, Maria Cristina Zingaretti<sup>1</sup>, Silvia Corvera<sup>2</sup> and <u>Saverio Cinti<sup>1</sup></u>

<sup>1</sup>Department of Experimental and Clinical Medicine, University of Ancona (Politecnica delle Marche), 60126 Ancona, Italy

<sup>2</sup> Program in Molecular Medicine, University of Massachusetts Medical School, Worcester, MA 01605, USA

Adipose tissue expansion involves the enlargement of existing adipocytes, the differentiation of adipocyte progenitors, and the development of the supporting vascular network. Although some data suggest that the adipocyte progenitors reside in the vasculature of the adipose tissue, their identity is not completely clear [1,2]. Here we address the hypothesis that a population of adipocytes derives from an endothelial cell (EC) lineage.

We performed a detailed morphological analysis in developing murine WAT and BAT in order to highlight the features of adipocyte precursors. In addition, we used the VE-Cadherin-Cre/R26R mouse model to address the relationship between vascular ECs and adipose cells development. This lineage tracing model allowed the identification of cells that express the EC gene VE-Cadherin at any point during differentiation. Finally, we analyzed capillary sprouts arising from human subcutaneous fat tissue to evaluate the hypothesis that ECs forming these structures possess the capacity to transform into adipocytes.

Ultrastructural analysis of discrete areas of intense adipogenesis, that we designated vasculo-adipocytic islets, revealed the presence of rare endothelial-pericytic cells that could represent an intermediate developmental step between the EC and the preadipocyte stage. Lineage tracing experiments using the VE-cadherin promoter revealed the expression of reporter genes in ECs, preadipocytes and adipocytes in white and brown fat depots. Furthermore, capillary sprouts (which have predominantly EC characteristics) from human adipose tissue were found to express Zfp423, a recently identified marker of preadipocyte determination [3]. In response to PPAR $\gamma$  activation the ECs lost progressively their structural and molecular characteristics, and formed structurally and biochemically defined adipocytes.

We report morphological and genetic evidence that adipocytes in white and brown fat depots originate from cells that display endothelial characteristics and this is in accordance with the results published by other researchers [4] and also with previous works performed in our lab [5].

## References

- [1] Rodeheffer et al. (2008). Identification of white adipocyte progenitor cells in vivo. Cell 135: 240-249.
- [2] Tang et al. (2008). White fat progenitor cells reside in the adipose vasculature. Science 322: 583-586.
- [3] Gupta et al. (2010) Transcriptional control of preadipocyte determination by Zfp423. Nature. 2010 Mar 25;464(7288):619-23.
- [4] Gupta et al. (2012) Zfp423 Expression Identifies Committed Preadipocytes and Localizes to Adipose Endothelial and Perivascular Cells. Cell Metab. 15: 230–239.
- [5] Cinti et al. (1984). A morphological study of the adipocyte precursor. J Submicrosc Cytol 16: 243-251.

Keywords: Adipose stem cells, adipogenesis, white adipose tissue, electron microscopy.