Journal of Theoretical Biology 429 (2017) 61–81

Contents lists available at ScienceDirect

Journal of Theoretical Biology

journal homepage: www.elsevier.com/locate/jtbi

Simple mechanical cues could explain adipose tissue morphology

D. Peurichard [a], F. Delebecque [b,c], A. Lorsignol [d], C. Barreau [d], J. Rouquette [e,f], X. Descombes [g], L. Casteilla [d], P. Degond [h,*]

[a] Faculty of mathematics, Wien university, Oskar-Morgenstern-Platz Wien 1,1090, Austria
[b] Université de Toulouse; UPS, INSA, UT1, UTM, Institut de Mathématiques de Toulouse, Toulouse F-31062, France
[c] CNRS, Institut de Mathématiques de Toulouse UMR 5219; Toulouse F-31062, France
[d] Université de Toulouse, CNRS ERL5311, EFS, INP-ENVT, Inserm U1031, UPS, BP 84225, Toulouse Cedex 4 F-31 432, France
[e] University of Toulouse, ITAV-USR3505, Toulouse, France
[f] CNRS, ITAV-USR3505, Toulouse, France
[g] Université Côte d'Azur, INRIA, I3S, France
[h] Department of Mathematics, Imperial College London, London SW7 2AZ, United Kingdom

ARTICLE INFO

Article history:
Received 15 February 2017
Revised 20 June 2017
Accepted 22 June 2017
Available online 23 June 2017

Keywords:
Adipose tissue
Mathematical modeling
Agent-based model
Image segmentation
Morphogenesis
Lobule-like structure

ABSTRACT

The mechanisms by which organs acquire their functional structure and realize its maintenance (or homeostasis) over time are still largely unknown. In this paper, we investigate this question on adipose tissue. Adipose tissue can represent 20 to 50% of the body weight. Its investigation is key to overcome a large array of metabolic disorders that heavily strike populations worldwide. Adipose tissue consists of lobular clusters of adipocytes surrounded by an organized collagen fiber network. By supplying substrates needed for adipogenesis, vasculature was believed to induce the regroupment of adipocytes near capillary extremities. This paper shows that the emergence of these structures could be explained by simple mechanical interactions between the adipocytes and the collagen fibers. Our assumption is that the fiber network resists the pressure induced by the growing adipocytes and forces them to regroup into clusters. Reciprocally, cell clusters force the fibers to merge into a well-organized network. We validate this hypothesis by means of a two-dimensional Individual Based Model (IBM) of interacting adipocytes and extra-cellular-matrix fiber elements. The model produces structures that compare quantitatively well to the experimental observations. Our model seems to indicate that cell clusters could spontaneously emerge as a result of simple mechanical interactions between cells and fibers and surprisingly, vasculature is not directly needed for these structures to emerge.

Author Summary

Because of the key role of adipose tissue in energy homeostasis and associated diseases, there is a great deal of interest in understanding the biology of this tissue. Very little is known about the key to understanding its structuration as lobules. We postulate that lobule emergence is the result of a self-organization process driven by bidirectional mechanical interactions between adipocytes and fibers. We test this hypothesis by means of a 2D individual based model of interacting adipocytes and fiber elements. Indeed, our model produces structures that compare quantitatively well to the experimental observations. This clearly shows that cell clusters of adipose tissue could spontaneously emerge as a result of simple mechanical interactions, with no direct involvement of vasculature.

1. Introduction

White adipose tissue (WAT) is the main energy store of the organism. It is interconnected with all physiological functions via its endocrine functions. It plays a key role in the energy homeostasis and weight of the organism. It is a highly plastic tissue composed of differentiated adipocytes that are able to store and release fatty acids as well as to secrete numerous cytokines and hormones (Ouchi et al., 2011). Mature adipocytes represent only 40 to 60% of the whole cell population. The other cells form a heterogeneous population named the stroma-vascular fraction (SVF). Adipocyte progenitors are present in the SVF throughout adult life (Sepe et al., 2011). They can proliferate and/or be recruited according to physiological or pathological situations, participate in the turnover

* Corresponding author.
E-mail addresses: pdegond@imperial.ac.uk, pierre.degond@gmail.com (P. Degond).

http://dx.doi.org/10.1016/j.jtbi.2017.06.030

of adipocytes and are also believed to be supporting cells. Because of their important role and due to the explosive worldwide development of obesity, the molecular pathways driving adipocyte differentiation are now well investigated and described (Cristancho and Lazar, 2011, Ailhaud, 1999, Hemmingsen et al., 2013). In contrast, the global organization at the tissue scale is poorly understood. Since Wassermann's work in 1960 (Wasserman, 2011), very few investigations have been performed at this scale. These seminal investigations revealed that adipose tissue is constituted of distinct lobules containing clusters of adipocytes. Moreover, observing its development, Wassermann described the emergence of mature WAT from primitive structures constituted of an unstructured fiber network containing endothelial cells and fibroblast-like cells. The latter are believed to be preadipocytes. In adult adipose tissue, lobules housing adipocytes are separated from each other by well-structured separations (or septa) composed of extracellular matrix (ECM) Napolitano (1963). Thereafter the number of lobular units seems to remain approximately constant. In excessive development of adipose tissue occurring during obesity, increased fibrosis (formation of excess fibrous tissue) is observed and many reports associate these changes with adipocyte dysfunctions (Divoux and Clement, 2011; Sun et al., 2013). This suggests that a proper maintenance of adipose tissue architecture is critical for its normal functionality.

Because the global architecture of adipose tissue and its organization into lobules are robust throughout adult life and seem to be fundamental elements of adipose tissue homeostasis, modeling the process of lobule emergence will greatly improve our understanding of adipose tissue biology and plasticity in physiological or pathological conditions. Numerous models of tissue morphogenesis can be found in the literature, describing the emergence of self-organization of cells and fibers. Due to their simplicity and flexibility, the most widely used models are Individual Based Models (IBM) (see Drasdo (2003), Hwang et al. (2009) and references therein). They describe the behavior of each agent (e.g. a cell or a fiber element) and its interactions with the surrounding agents over time. Due to the high computational cost of IBM, mean-field kinetic or continuous models, which are more efficient to describe the large scales, are often preferred. All these models include one or several of the following interactions: (i) cell/cell, (ii) cell-fiber and (iii) fiber-fiber interactions. Models of interacting cells moving in ECM-free media such as Drasdo and Höhme (2005) focus on interactions of type (i). Based on the mechanisms reviewed in Friedl and Bröcker (2000), a wide variety of models incorporating interactions of type (ii) have been proposed such as: (a) mechanical models Murray et al. (1983), (b) chemotaxis-type models (Ambrosi et al. (2005); Lushnikov et al. (2008) and references therein), where cell motion is driven by chemical gradients or (c) models of contact guidance (Guido and Tranquillo, 1993) (see Dickinson (2000); Hillen (2006); Hillen et al. (2010)) where the ECM gives directional information for cell motion. However, how the processes are coordinated to produce directed motion is not well understood. Fiber-fiber interactions have been explored in Alonso et al. (2014), where a model of a fibrous network composed of cross-linked fiber elements is proposed. Other authors treat the fibrous network as a continuum, such as a porous medium (Taber et al., 2011) or an active gel (Joanny et al., 2007) for instance. However, the literature so far provides little clues on the mechanisms underlying contact guidance or fiber self-organization. In the present paper, we demonstrate that directionally organized cell and fiber structures can emerge without appealing to contact guidance or fiber directional interactions, as a result of simple mechanical interactions between the cells and the fiber network. To test this hypothesis qualitatively, it is sufficient in a first instance to consider a two-dimensional model, which we do for reasons of simplicity and computational efficiency. Our model is of more microscopic nature than previously proposed mechanical models (Murray et al., 1983; Shraiman, 2005) and aims at describing the emergence of the lobular structures observed in adipose tissue. Our goal is to test the scenario that, due to the fibers resisting the pressure induced by the growing adipocytes, the latter are forced to regroup into clusters. Adipocyte clusters in turn force the fibers to merge into a well-organized network. To validate this scenario, we developed a two-dimensional IBM modelling adipocytes interacting with ECM fiber elements. The model and experiment data showed strikingly similar lobule-like structures and revealed that vasculature was not needed for lobular self-organization to emerge, although vasculature is a proven key factor of adipogenesis (Corvera and Gealekman, 2014).

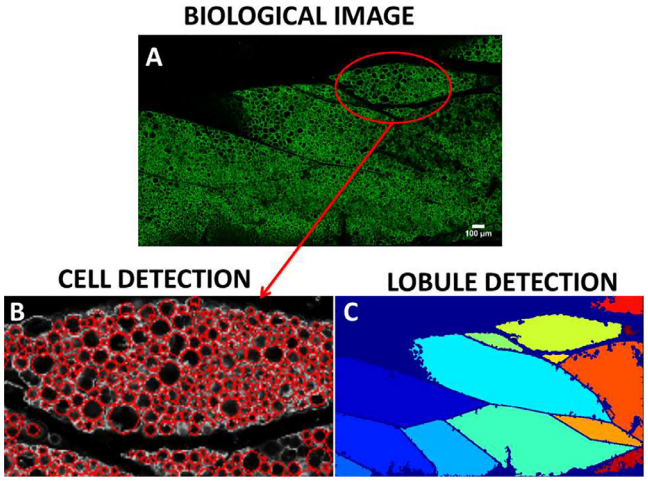

Fig. 1. Adipose tissue imaging (A) 2D Image of a part of mouse sub-cutaneous adipose tissue. Lipid droplets were immunostained for perilipin (green). ECM between adipocyte clusters appears in black. (B) Magnification of the part enclosed by the red line on image (A), showing the result of cell detection. Cells appear as red circles. (C) Image (A) after lobule detection. Detected lobules have been distinguished by different colors. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

2. Material and methods

2.1. Experiments and image processing

Fig. 1 shows part of a sub-cutaneous adipose tissue from an adult mouse. The adipocytes were visualized by immuno-staining of perilipin, a protein that surrounds the unilocular lipid droplets. In Fig. 1A, the ECM fiber network appears in black as a background. This picture clearly reveals the organization of the adipose tissue in lobules. A 3D image of one isolated lobule is shown in supplementary information. We implemented classical image processing methods to extract the centers and radii of the cells (Fig. 1B) and the different lobules (Fig. 1C) (see Appendix D for details). The quality of the cell and lobule segmentation methods was carefully checked.

2.2. Description of the model

We postulated that, in WAT, the agents contributing the most to mechanical balance were the ECM fibers and the adipocytes. The ECM was discretized into unit fiber elements consisting of line segments of fixed and uniform lengths represented by their centers and their directional unit vectors. We supposed that two fiber elements that crossed each-other could form a link, thereby creating a longer fiber. The cells were described as 2D spheres represented by their centers and radii. At any given time, the two sets