Modelling of adipocytes dynamics.

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Obesity is a worldwide major public health issue that doubled since 1980 and affects nowadays almost two billion of adults considered as overweight and 600 million considered as obese.Strikingly, obesity is the most prevalent cause for the development of cardio-metabolic diseases (cardiovascular disease, type 2 diabetes, and liver diseases) as well as cancer, increasing mortality and morbidity and justifying the need for intensive research and intervention policy.

Obesity is characterized by an increase in adipose tissue (AT) mass. This expansion of AT is a complex process which requires steps of proliferation, differentiation and maturation of the cells from the adipocytes lineage [1]. Indeed, within AT, vascular-resident adipose progenitor cells (APCs) proliferate and under specific signals differentiate into pre-adipocytes. Pre-adipocytes also expand through proliferation before to differentiate into small mature adipocytes [2, 3]. Mature adipocytes have an impressive capacity of expanding their volume by more than 30-fold through triglyceride accumulation in lipid droplets, which are liquid [4],but stiffer than the cytosol. Ultimately, one lipid droplet occupies most of the cytoplasm and thereby contributes to the stiffness of AT.The mechanical forces generated by this large lipid droplet in hypertrophic adipocytes may limit their maximum diameter size. The hypertrophic adipocytes may also mechanically stimulate the differentiation of APCs and preadipocytes through activation of their mechanoreceptors to recruit new adipocytes to store the excess of lipids [5]. Mature adipocyte size is not only critical for adipogenesis initiation but also for adipocyte functions. Indeed, hypertrophic adipocytes have less ability to properly store lipids resulting in spillover of lipids and excessive fat deposition in non-adipose tissues that contribute to the development of cardio-metabolic diseases. Although there is growing evidence that impaired AT expandability plays a pivotal role in obesity-related cardio-metabolic diseases, the molecular and cellular basis of this phenomenon is far from being understood. This could be partly due to the complexity of the process. Indeed, the expansion of AT depends on a large number of parameters including the rate of APCs and pre-adipocytes proliferation/differentiation/death, the mechanical feedback loop of adipogenesis stimulation, the size of the adipocytes and the kinetic of their death. Due to its pathological implication, it seems now crucial to develop innovating approaches to solve this lack of knowledge. Mathematical modeling can be used to tackle this important question. Indeed, such an approach can in an analytic manner integrate all the parameters into equations and then determine the rate limiting parame-

ters required to develop a functional adipose tissue. Among the different parameters, the mechanical feedback loop of adipogenesis stimulation is a pivotal parameter that could control the ability of adipose tissue to expand through the recruitment of new adipocytes.

1 A 0D model of adipocytes dynamics without mechanical interaction

We think of the process as a compartment model with three populations of cells: mesenchymal, pre-adipocytes and adipocytes, the latter population being structured by the size of the cells. Let $t \mapsto m(t)$ and $t \mapsto p(t)$ stand for the number of mesenchymal, and pre-adipocytes, respectively, which depend on the time variable $t \geq 0$. Adipocytes are described by their radius distribution function $(t, r) \mapsto a(t, r)$. Mesenchymal and pre-adipocytes are subjected to proliferation and mortality mechanisms. Furthermore, mesenchymal cells differentiate into pre-adipocytes, while pre-adipocytes differentiate into adipocytes. The mutation of pre-adipocytes gives rise to adipocytes with radius $r^\star \geq 0$, and $r^\star$ will be the minimal radius within the adopicytes population. Eventually, adipocytes are subjected to natural mortality and to a dynamic of change of radius, the mechanisms of which are embodied into a growth rate function $(t, r) \mapsto V(t, r)$. Roughly speaking the variation of the radius is described by the ODE

$$\frac{\mathrm{d}}{\mathrm{d}t} R(t) = V(t, R(t)).$$

As it will be detailed below, we assume the existence of a critical size $r_c > 0$, which actually depends on time, beyond which adipocytes shrink instead of growing. Hence the parameters of the model can be collected as follows

α, α'	proliferation rates for m, p, resp.
β, β'	differentiation rates for m and p, resp.
γ, γ', γ''	mortality rates for m, p and a, resp.
$r^\star$	emergence size of adipocytes (minimal size)
r_c	typical size at which adipocytes shrink instead of growing
$V(t, r)$	growth rate of an adipocyte of radius r at time t

The unknowns depend on the time variable $t \in [0, +\infty)$ and, for the adipocyte distribution, on the radius variable $r \in [r^\star, +\infty)$. $\int_{r^\star}^{+\infty} a(t, s)\,\mathrm{d}s$ represents the total number of adipocytes, at time t. For further purposes, let us introduce

$$\bar{r}(t) = \frac{\displaystyle\int_{r^\star}^{+\infty} s\ a(t, s)\,\mathrm{d}s}{\displaystyle\int_{r^\star}^{+\infty} a(t, s)\,\mathrm{d}s}, \qquad \text{the mean radius of adipocytes at time } t$$

$$S(t) = 4\pi \int_{r^\star}^{+\infty} s^2\ a(t, s)\,\mathrm{d}s, \qquad \text{the total surface of functional adipocytes at time } t.$$

We account for feedback mechanisms by assuming that the mutation rates β and β' are functions of $\bar{r}$, typically with a sigmoid shape that reproduce threshold effects:

$$\beta(\bar{r}) = \frac{\beta_0\ \bar{r}^n}{\beta_1 + \bar{r}^n} \text{ and } \beta'(\bar{r}) = \frac{\beta_0'\ \bar{r}^m}{\beta_1' + \bar{r}^m}$$

with $\beta_0 > 0$, $\beta_0' > 0$, $\beta_1 > 0$, $\beta_1' > 0$ and $n, m \in \mathbb{N}$. For describing the growth rate, we consider that the variation of volume with respect to time is given by the flux of food, which is proportional to the ratio of the surface of the considered adipocyte over the total surface of all adipocytes, leading to the following relation :

$$V(t,r) = \frac{k(t)}{4\pi \displaystyle\int_{r^\star}^{r_c} s^2 a(t,s)\,\mathrm{d}s} = \frac{k(t)}{S(t)}, \tag{1}$$

which holds as far as the radius is not too large. On the contrary, large cells cannot continue to grow, and instead the largest shrink. We describe these effects with a smooth transition that involves two parameters $\epsilon_1, \epsilon_2 > 0$: we adopt the following formula for the growth rate

$$V(t,r) = \frac{k(t)}{S(t)}\mathbf{1}_{r<r_c-\epsilon_1} + \Phi(t,r)\mathbf{1}_{r_c-\epsilon_1\le r<r_c+\epsilon_2} - \lambda(t)\mathbf{1}_{r\ge r_c+\epsilon_2},$$

with $t \mapsto \lambda(t)$ a given positive function, and Φ joins smoothly the cut-off functions.

The evolution of the population of mesenchymal, pre-adopicytes and adipocytes is finally governed by the following set of equations

$$\begin{aligned}
&\frac{\mathrm{d}m}{\mathrm{d}t}(t) = -\gamma m(t) + \alpha m(t) - \beta(\bar{r}(t))m(t),\\
&\frac{\mathrm{d}p}{\mathrm{d}t}(t) = -\gamma' p(t) + \alpha' p(t) - \beta'(\bar{r}(t))p(t) + \beta(\bar{r}(t))m(t),\\
&\frac{\partial a}{\partial t}(t,r) + \frac{\partial}{\partial r}\left(Va\right)(t,r) = -\gamma'' a(t,r).
\end{aligned} \tag{2}$$

The system is complemented by initial data

$$m(0) = m_{\text{Init}} \ge 0, \qquad p(0) = p_{\text{Init}} \ge 0, \qquad a(0,r) = a_{\text{Init}}(r) \ge 0. \tag{3}$$

Since $V(t, r^\star)$ is positive, we also need to prescribe the boundary condition for a when $r = r^\star$; this is where we take into account the mutation of the pre-adipocytes into adipocytes:

$$V(t,r^\star)\ a(t,r^\star) = \beta'(\bar{r}(t))\ p(t). \tag{4}$$

For the largest adipocytes, the growth rate is negative, and we simply assume that

$V(t,r)\ a(t,r) = 0$ for $r > r_c + \epsilon_2$ large enough.

2 Adding response to mechanical stimuli

We will extend the previous model by adding a spatial dependence to mimic the adipose tissue. All three variables m, p and a will now also depend on the space variable $x \in \Omega \subset \mathbb{R}^n$ ($n = 2$ or 3, Ω bounded): $m(t,x)$, $p(t,x)$ are functions from $\mathbb{R}_+ \times \Omega$ in $\mathbb{R}_+$ while $a(t,x,r)$ is a function $\mathbb{R}_+ \times \Omega \times [r^*, +\infty[$ in $\mathbb{R}_+$.

One new scalar field $q(.)$ from Ω into $\mathbb{R}$ will be introduced. In the simplest interpretation, q can be seen as the local tissue pressure grossly proportional to the tissue stiffness. q is larger where adipocytes have large sizes. We assume this pressure is instantly propagated into the whole tissue. The local pressure $q: \Omega \to \mathbb{R}$ can be modelled with:

$$\begin{cases} \triangle_x q(t,x) = F(a(t,.,x)) & \text{on } \Omega \\ q = 0 & \text{on } \partial\Omega \end{cases}$$

with F a function of the size distribution of adipocytes that represents pressure source due to the presence of adipocytes affecting the tissue stiffness. Typically we could use a smooth increasing function f, with $f(r^*) = f'(r^*) = 0$ and

$$F(a(t,.,x)) = f(\bar{r}(t,x)) \quad \text{with} \quad \bar{r}(t,x) = \frac{\int_{r^*}^{+\infty} s \times a(t,s,x) ds}{\int_{r^*}^{+\infty} a(t,s,x) ds}$$

In this new approach, the parameters γ, α, β, γ', α', β' and γ'' might all be functions of the value of q (and thus also depend on space). At first, we can however assume that only β and β' depend on q, we can also hypothesize that β and β' are increasing functions of q. Several other adjustments of the 0D model should be needed to close the spatial model; moreover data from biologist to evaluate more precisely the function F and the dependence on q of the different parameters for differentiation should be available at the end of June 2018.

The goal of the project is to understand the dynamics of adipocytes both in time and space through mathematical analysis and numerical simulations, and to compare the model predictions with data acquired by biologists from C3M laboratory in Nice.

3 Support, etc.

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