Disregulation of tissue homeostasis in a two cell-type system

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Biological systems operate far from thermodynamic equilibrium, relying on the exchange of matter and energy with the environment to perform specific functions. Despite operating in noisy environments, biological systems can maintain physiological variables in an optimal operational regime, a property known as homeostasis. Nevertheless, homeostasic properties can be altered in response to certain conditions, such as disease. It is thus crucial to understand the disregulation of homeostasis in order to be able to steer recovery after a perturbation like disease.

Here, we study the disregulation of tissue homeostasis resulting from intrinsic and extransic perturbations using a combination of theoretical and experimental approaches. In particular, we focus on an established *in vitro* minimal model of a tissue, corresponding to co-cultures of fibroblasts and macrophages, two cell types found in most mammalian tissues that form stable circuits [1, 2]. In addition to growth factors secreted by the other cell type, these cells require micronutrients supplied as part of the cell culture medium in order to grow and proliferate.

A crucial micronutrient required for proper mitochondrial function, and hence for proliferation, is iron. However, free (labile) iron is highly reactive, becoming toxic unless stored in a non-reactive form, a task performed by ferritin, a molecule that stores iron in a non-reactive form and is able to release it when required for cellular functions [3].

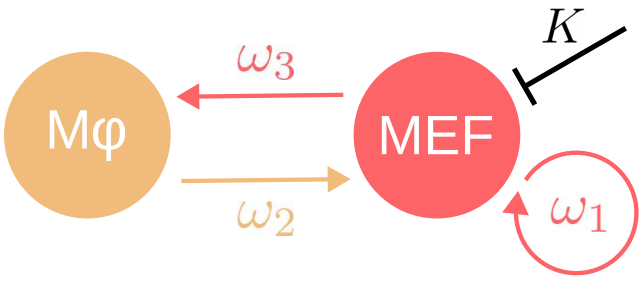

Fig. 1. Cartoon of the theoretical model depicting the interactions between fibroblasts (MEF) and macrophages (Mϕ).

In this work we study the disregulation of homeostasis in the fibroblasts-macrophages cell circuit resulting from intrinsic and extrinsic perturbations, corresponding respectively to ferritin knock-outs and to the addition of supplemental iron to the cell culture media. Our experimental results show that when both cell types lack ferritin iron toxicity leads to the extinction of both cell types. However, when only fibroblasts lack ferritin, the dynamics are rescued by the interactions between the two cell types, reaching a steady-state characterised by the coexistence of fibroblasts and macrophages.

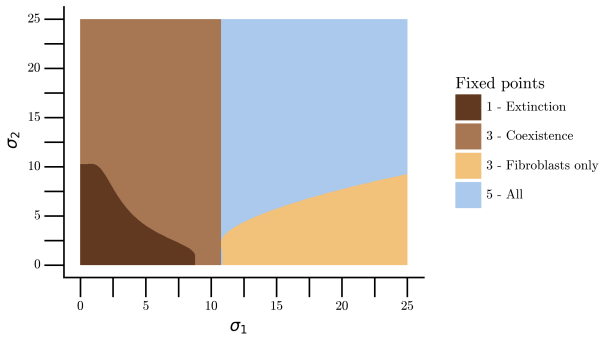

Fig. 2. Phase diagram of the system as a function of the strength of the ferritin-mediated regulation of the intracelular iron pool of fibroblasts σ_1 and macrophages σ_2. Color indicates the number of fixed points of the dynamics with non-negative concentration of fibroblasts and macrophages.

Our experimental findings are supported by theoretical modelling of the dynamics of the concentration of fibroblasts, macrophages and their respective intracellular free iron pools (Fig. 1). We show that the steady-state of the dynamics is determined by two effective parameters corresponding to the asymptotic death to proliferation ratios of fibroblasts and macrophages. Furthermore, for biologically-sensible values of the model parameters, our model phenomenologically reproduces the outcome of the different experimental conditions by adequately tuning the strength of the ferritin-mediated regulation of the intracelular iron pool. (Fig. 2).

Taken together, we have shown using a combination of a minimal *in vitro* system and theoretical modelling, how cellular interactions can lead to the restoration of tissue homeostasis even in the presence of strong intrinsic and extrinsic perturbations.

[1] X. Zhou et al., *Circuit design features of a stable two-cell system*, Cell **172(4)**, (2018).

[2] M. Adler et al., *Endocytosis as a stabilizing mechanism for tissue homeostasis*, PNAS **115(8)**, (2018).

[3] B. Blankenhaus et al., *Ferritin regulates organismal energy balance and thermogenesis*, Molecular Metabolism **24**, (2019).