Mathematical modelling of the inflammation process in osteoarthritis

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INTRODUCTION: Osteoarthritis (OA) is a progressive disorder locally involved in the whole joint with low-grade inflammation. As a prominent risk factor, obesity is tightly associated with the onset and development of OA due to the increase in body weight and the abnormal level of adipokines. Adipokines are OA biomarkers that regulate inflammation in either synovium or cartilage. However, the molecular mechanisms regulating inflammation related obesity and its direct effect on joint damage are still unclear. This study aims to develop a mathematical model to analyze the dynamics of the inflammation mediated by adipokines and the effects of obesity on inflammation.

METHODS: A three-dimensional adipokine-mediated inflammation model (Fig. 1) was developed based on a cartilage inflammation model produced by Baker et al. [1]. In this adipokine-mediated model, the inflammation is mainly regulated by pro- and anti-inflammatory cytokines interacting with adipokines. The adipokine production is dependent on the level of obesity measured by Body Mass Index (BMI). Hill functions [2] are used to describe the feedbacks (stimulation and inhibition) between mediators. To reduce the complexity of parameters, the model is nondimensionalized through scaling.

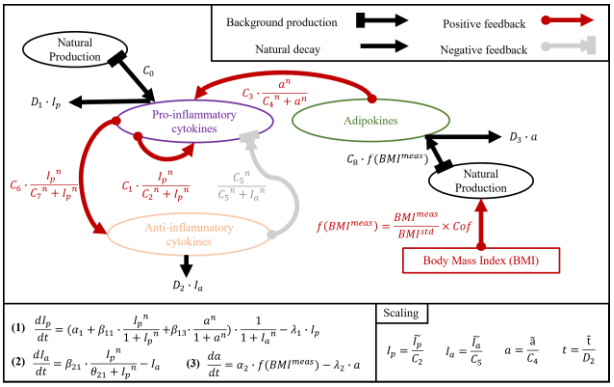

Fig 1. *Inflammation network mediated by obesity.*

RESULTS: Without a damage stimulus, cytokines and adipokines are in steady state in both the non-obese and obese states, albeit at a higher level for the obese state (Fig. 2). With a damage stimulus, anti-inflammatory cytokines are recruited to bring down pro-inflammatory cytokines but they stay at a high level and oscillatory in the case of the obese state. Three types of inflammatory dynamics are predicted (Fig. 3): healthy homeostasis; bistable inflammation; and persistent chronic inflammation, which agrees with [1]. The increase of adipokine production can result in a loss of the bifurcation so that the system is monostable in inflammation. A threshold of 0.04 for the background adipokine production rate (α_2) leads to stable inflammation (Fig. 3f).

DISCUSSION: A higher adipokine production results in the loss of bifurcations in the obese system by elevating the parameter (α_2). This suggests that obesity can increase the risk of inflammation regardless of the mechanical damage, which is consistent with the comparison of obese and non-obese system behaviors after a damage stimulus. Whilst increasing β_{11}, the parameter relevant to stimulating inflammation, can also reduce the bistability so that the healthy steady state is lost, this parameter does not vary with obesity level. The natural production of adipokine (α_2) is dependent on the obesity level, hence the threshold may explain the high risk of OA inflammation even without any damage.

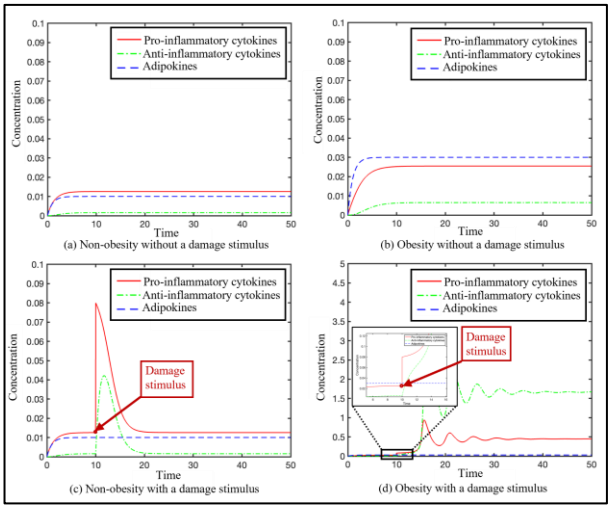

Fig 2. *The evolution of inflammatory activities.*

SIGNIFICANCE/CLINICAL RELEVANCE: This mechanistic computational model demonstrates the dynamics of inflammation regulated by adipokines and the impact of adipokine parameters. The inclusion of obesity in a mathematical model can give deeper insights into the mechanism of OA inflammation at a molecular level.

REFERENCES: [1] Baker M et al. Mathematical modelling of cytokines, MMPs and fibronectin fragments in osteoarthritic cartilage, J. Math. Biol., 75, 985–1024, 2017. [2] Santillán M. On the use of the hill functions in mathematical models of gene regulatory networks. Math. Model. Nat. Phenom., 3, 85–97, 2008.

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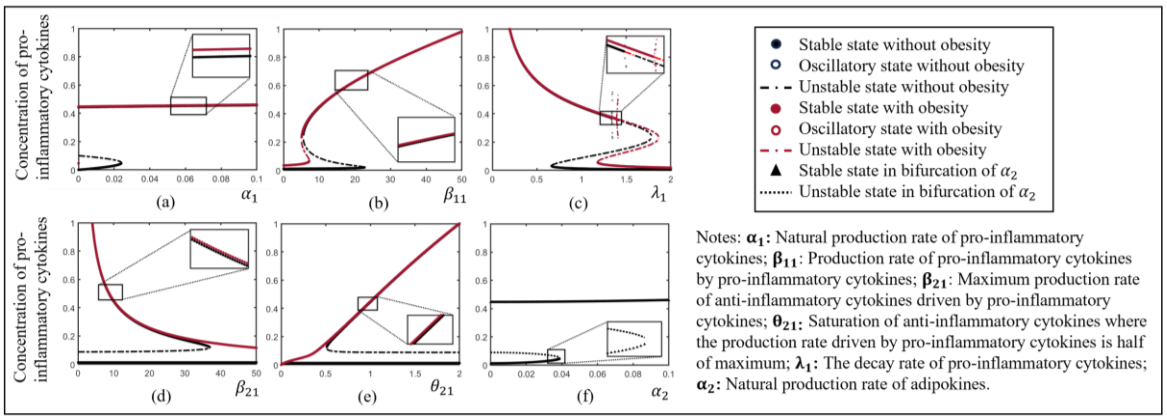

Fig 3. *Bifurcation diagrams(a)-(e) over the obese ($\alpha_2 = 0.01$) and nonobese ($\alpha_2 = 0.05$) systems and the bifurcation (f) of α_2.*