Multicellular modeling of MSC lineage progression under combination cytokine treatment for bone regeneration

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Abstract
Bone regeneration is a complex physiological process which involves many cytokines orchestrating to direct the mesenchymal stem cell (MSC) towards preosteoblast and eventually osteocyte. Previous studies concurred that sequential delivery of two cytokines (BMP-2 and IGF-1) with appropriate timing can well promote the final bone formation. Our recent comprehensive investigation revealed that this promotion is achieved via synergistic function of three bone-specific transcription factors, i.e. RUNX2, osterix and β-catenin, activated chronologically by the two cytokines. In the present work, we developed a multicellular model to simulate the MSC lineage commitment regulated by these transcription factors. At each time point, MSC can either differentiate into preosteoblast (OBp), or becomes quiescent (MSCq) and hence cannot enter the bone lineage anymore; likewise, the nascent OBp may further mature to active osteoblast (OBa) or get quiescent again. We employ a novel system of ordinary differential equations (ODEs) to describe the dynamic 'flow' between the mentioned lineage compartments. The major novelty of this system lies in the dynamic coefficients involved in the equations, reflecting dynamic cell proliferation, differentiation and quiescence rates. These time-varying rates can be estimated from the concentration change of different transcription factors indicative of related cytokines delivered. The simulation results well recapitulated the experimental observations and accurately predicted the optimal temporal combination of dual cytokines for bone remodeling. Our model also revealed how the cytokines interact to promote optimal bone formation. The success largely depends on deep mining of information from available time-point data, together with sufficient integration of well-established knowledge of molecular and cellular biology. We expect our modeling strategy can also be used to explore the best dosage combinations of multiple cytokines and, can be parallel applicable to other related research involving dual cytokine deliveries.