

Temporal dynamics of macrophages plasticity in the bone microenvironment

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Tumour associated macrophages have long been implicated in the progression of primary solid malignancies including prostate cancer. Metastatic prostate cancer typically manifests in the bone where it induces painful osteogenic lesions that are incurable. Bone is naturally rich in myeloid derived macrophages whose temporal polarization into pro- (M1) and anti-inflammatory (M2) phenotypes is critical for regulating the program of bone injury repair mediated by bone resorbing osteoclasts (OCL) and bone building (OBLs). However, the dynamics of macrophage polarization in the context of bone metastatic prostate cancer is underexplored and difficult to address with traditional biological approaches. In order to address it we built a mathematical model describing bone resident cell population dynamics during bone injury response through a set of coupled ordinary differential equation (ODE). We informed this model by analyzing macrophage plasticity *in vivo* subsequent to intratibial injury. Bone marrows were isolated at several time points and profiled by flow cytometry for pro- and anti-inflammatory macrophage content. Contralateral tibias were analyzed for bone volume, osteoblast and osteoclast numbers. The ODE model was able to predict experimental observations of M1/M2, OBL, OCL and bone dynamics. Generation of the ODE model required testing a number of assumptions regarding macrophage polarization behaviour. For example, it is unknown whether M1 resolve at the initial stages of bone injury repair through death, or by re-polarizing into M2. For each aspect, competing mechanistic assumptions were proposed and simulated mathematically by sets of ODEs. The best fitting assumptions for each aspect were integrated into a comprehensive ODE model to fully describe the dynamics of the bone resident cell populations during bone repair. This experimentally validated model is now being exploited to address how bone population dynamics respond to metastatic prostate cancer cells and subsequently identify the resultant impact on bone formation and cancer growth.

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