Tumor-Host Tissue Interactions Through MSCs: Implications for Cancer Cachexia

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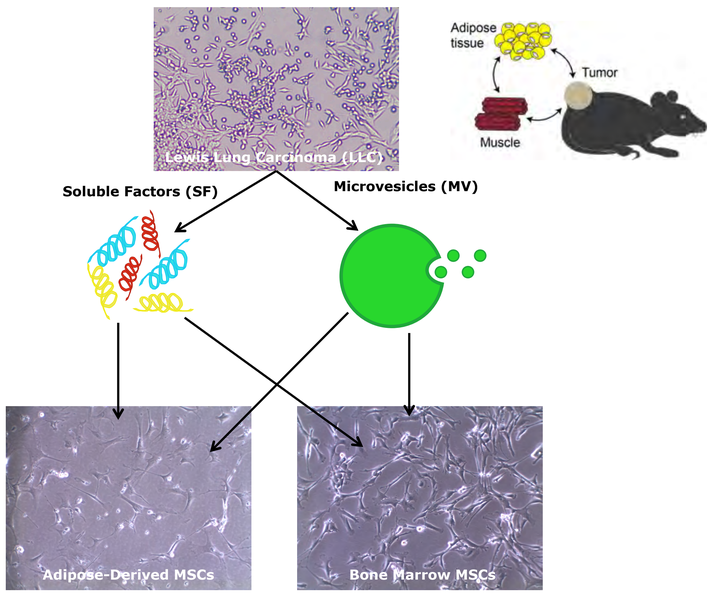
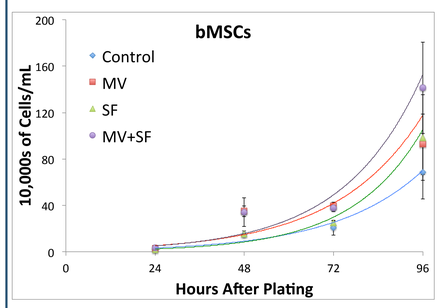
Abstract

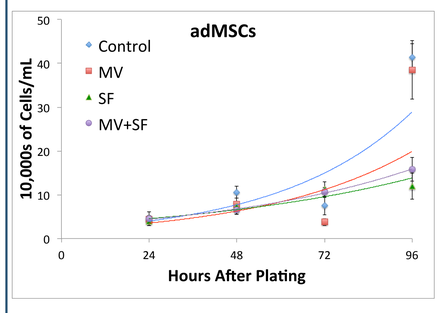
- Cancer cachexia is a serious complication that occurs in up to 50% of patients. It is defined as a severe loss of body mass (mostly in fat and muscle). Diagnosis commonly occurs after a patient loses more than 5% weight in 6 months
- We aim to elucidate the role of Mesenchymal Stem Cell (MSC) recruitment & reprogramming by cancer as a part of cachexia development
- MSCs are able to differentiate into a broad range of mature cell types, including myocytes & adipocytes, the tissues lost in cachexia
- We take a Systems Biology approach that integrates mathematics, bioinformatics, and experimental biology in order to study this complex phenomenon

General Experimental Setup



Proliferation

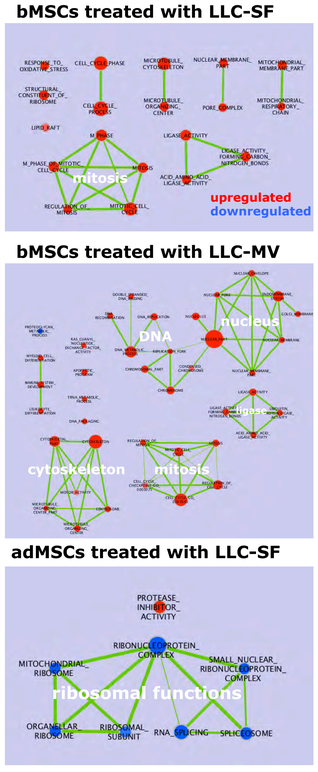




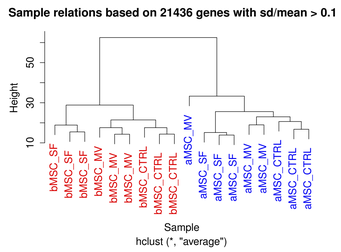
bMSCs treated with LLC-SF

bMSCs treated with LLC-MV

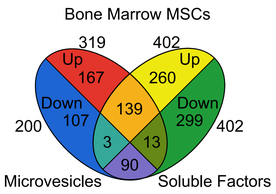
adMSCs treated with LLC-SF

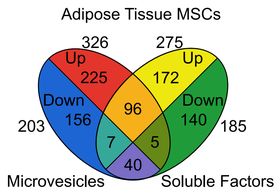


Differential Gene Regulation

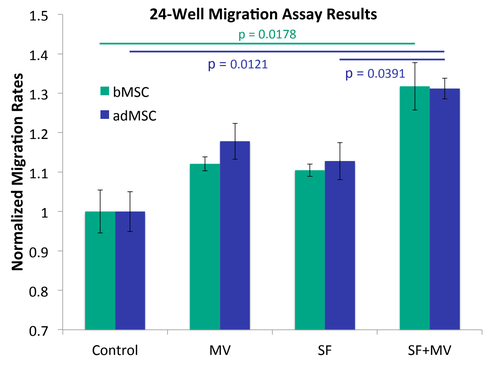


Note that:
- **upregulated functions in bMSC cells are consistent with growth curve results**
- **adMSCs treated with LLC-MV exhibited no functional changes that met the thresholds for significance**
- **the ribosomal functions of adMSCs treated with LLC-SF exhibit downregulation**



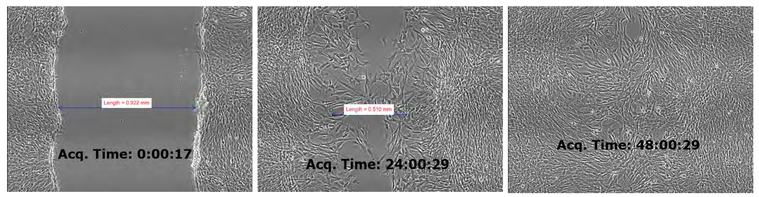


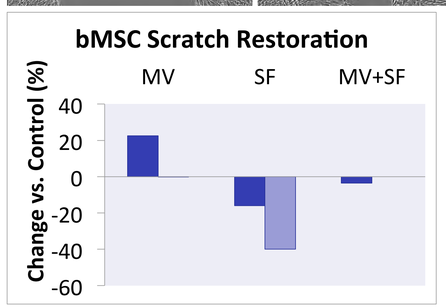
Migration



bMSC Scratch Assay

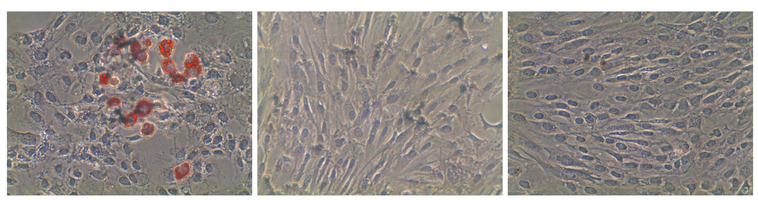
Images of Control Well (*Rate = .922mm / 60 hrs*)





bMSC Differentiation (Oil Red Staining)

grown in adipogenic differentiation media



no tumor factors **+ LLC-SF** **+ LLC-MV**

Mathematical Model

Host-Level ODE Model for Cachexia

$$muscle: \frac{dM}{dt} = \alpha M^{\mu - \nu T} - (\beta + \gamma T)(M + \eta T)$$

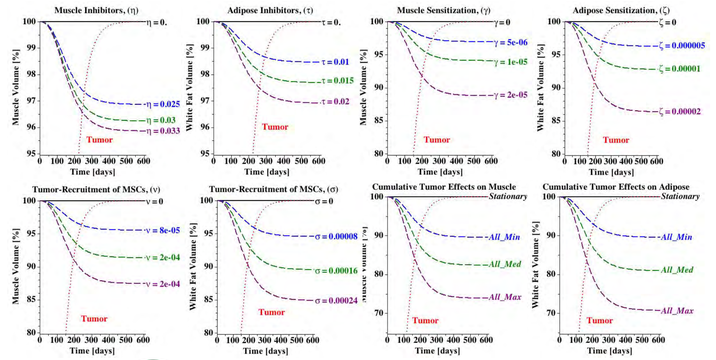
$$adipose: \frac{dW}{dt} = \xi W^{w - \sigma T} - (\delta + \zeta T)(W + \tau T)$$

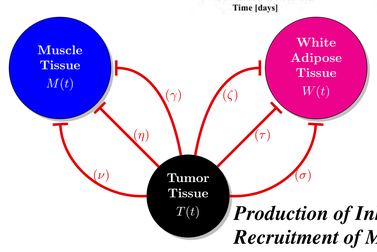
$$tumor: \frac{dT}{dt} = -\lambda T \ln\left(\frac{T}{T_{max}}\right)$$

(Gompertzian growth)

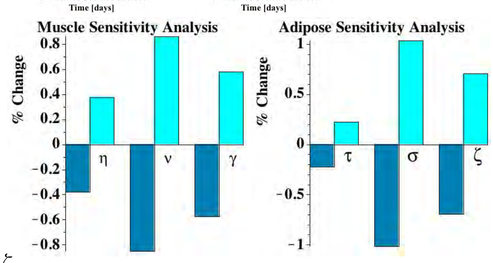
in M(t) & W(t),
+ terms model tissue growth
- terms model tissue loss

We chose the basic parameters ($\alpha, \beta, \xi, \delta, \mu, \omega$) to give an equilibrium solution at M=100% and W=100%, assuming a stem-cell fraction of 2.5% in muscle (μ) and 5% in white fat (ω). The other parameters were chosen to fit data from the literature and the preliminary results of the assays.



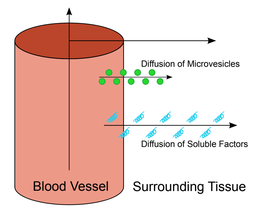


Production of Inhibitors are τ, η
Recruitment of MSCs are σ, ν
Sensitization to Inhibitors are γ, ζ



Tissue-Level Diffusion-Consumption Model for Tumor-Factors

1) $D^2(\nabla^2 n) - cn + s = \frac{\partial n}{\partial t}$ ⟶ 2) $n'' + \frac{1}{\rho}n' - \frac{cn}{D^2} + \frac{s}{D^2} = 0$ ⟶ 3) $u^2 z'' + uz' - u^2 z = 0$



***1)* is a generic diffusion-consumption equation for a stimulator or inhibitor inside the body. Assuming time-invariance and converting to cylindrical coordinates (as we want to model the diffusion from a blood vessel) transforms the equation into *2)*. Substituting u and z for n and ϱ respectively gives *3)*, a modified Bessel equation of order 0, for which exist two fundamental solutions.**

Discussion / Conclusions

Our preliminary data suggests the following conclusions:
- MV and SF of LLC-conditioned media each exert different influences on MSCs
- adMSCs and bMSCs respond quite differently to the same levels of exposure to tumor factors
- LLC-MV and -SF seem to inhibit adipocyte differentiation, which may help explain the loss of fat in cachexia patients
- Our model suggests that muscle/adipose tissue loss is most sensitive to tumor-induced alterations of their respective stem-cell ratios

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