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Supplemental information

Spatial heterogeneity in tumor adhesion qualifies collective cell invasion

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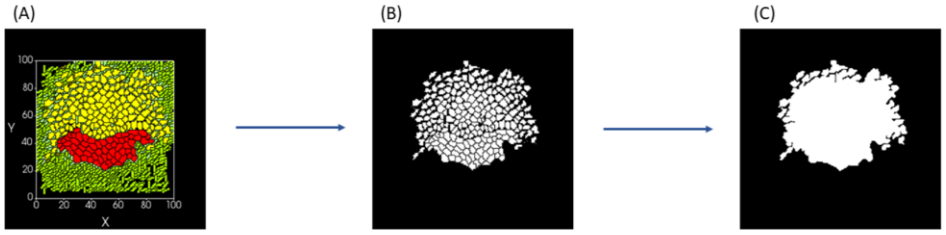

Figure S1: Image analysis and quantification of endpoint of simulation

(A) Endpoint of 'epithelial' & 'mesenchymal' simulations corresponding to Low HI I.

(B) Grayscale image consisting of only cells of the endpoint of simulation.

(C) Grayscale image after image morphological operations(strel, imdilate, imfill, bwareaopen in MATLAB) depicting the Area of largest cell cluster (ALC) and the remaining small cell clusters at the periphery contributing to Number of disconnected cell clusters (NDC).

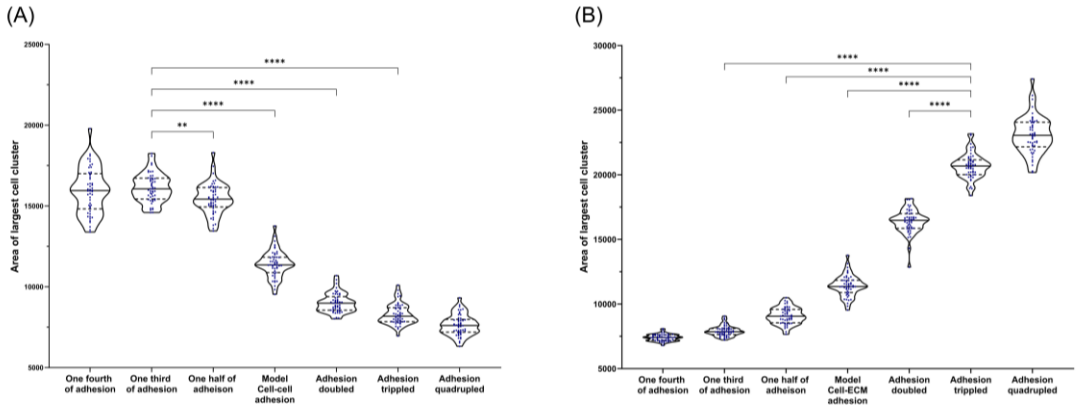

Figure S2: Monotonic decrement and increment in the area of largest cell cluster (measure of collective invasion) as cell-cell adhesion (left) and cell-ECM adhesion (right) is progressively increased respectively in homogeneous cell populations

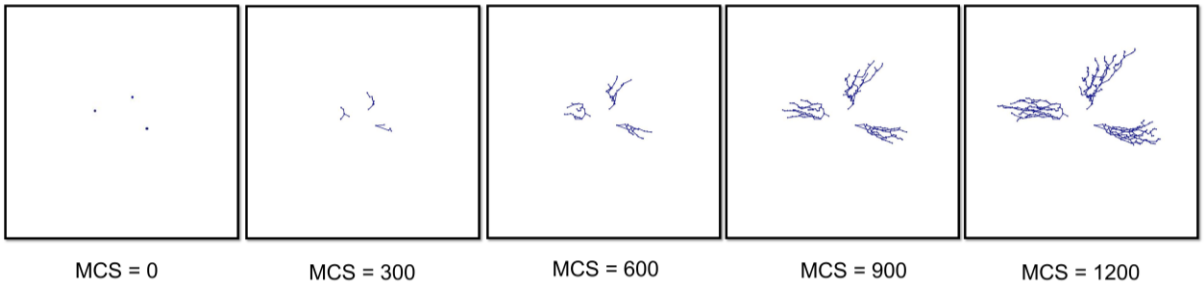

Figure S3: Tracking of three cells at equally spaced MC Steps of High HI case corresponding to low inter-subset cell adhesion showing migration tracks interspersed by cell division events.

Parameter values of simulations corresponding to model adhesion strengths of Fig1.

The parameter set consisting of six input parameters corresponding to homogeneous simulations undergoing collective cell invasion with model adhesion strengths (Middle simulation image of **Fig 1A** & **1B**) are given below. Collagen I here is same as extracellular matrix (ECM) referred in the main manuscript.

Cell-cell contact energy: 46
Cell-Collagen I contact energy: 46
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Parameter values of simulations corresponding to low inter-subset cell adhesion of Fig 2A.

Parameter values for **red** cells:

Cell-cell contact energy: (46/2) = 23 for 4-fold change case simulations,
(46/3) = 15.33 for 9-fold change case simulations,
(46/4) = 11.5 for 16-fold change case simulations.
Cell-Collagen I contact energy: 46
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Parameter values for **yellow** cells:

Cell-cell contact energy: (46*2) = 92 for 4-fold change case simulations,
(46*3) = 138 for 9-fold change case simulations,
(46*4) = 184 for 16-fold change case simulations.
Cell-Collagen I contact energy: 46
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Inter-subset cell contact energy between
red and yellow cells = max (23,92) = **92** (4-fold change),
= max(15.33,138) = **138** (9-fold change),
= max(11.5,184) = **184** (16-fold change).

Note: Maximum value of Contact energy corresponds to minimum adhesion strength

Parameter values of simulations corresponding to high inter-subset cell adhesion of Fig 3A.

Parameter values for **red** cells:

Cell-cell contact energy: (46/2) = 23 for 4-fold change case simulations,
(46/3) = 15.33 for 9-fold change case simulations,
(46/4) = 11.5 for 16-fold change case simulations.
Cell-Collagen I contact energy: 46
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Parameter values for **yellow** cells:

Cell-cell contact energy: (46*2) = 92 for 4-fold change case simulations,
(46*3) = 138 for 9-fold change case simulations,
(46*4) = 184 for 16-fold change case simulations.
Cell-Collagen I contact energy: 46
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Inter-subset cell contact energy between
red and yellow cells = min(23,92) = **23** (4-fold change),
= min(15.33,138) = **15.33** (9-fold change),
= min(11.5,184) = **11.5** (16-fold change).

Note: Minimum value of Contact energy corresponds to maximum adhesion strength

Parameter values of simulations corresponding to intra-subset cell-ECM adhesion of Fig 4A.

Parameter values for **red** cells:

Cell-cell contact energy: 46
Cell-Collagen I contact energy: (46/2) = **23** for 4-fold change case simulations,
(46/3) = **15.33** for 9-fold change case simulations,
(46/4) = **11.5** for 16-fold change case simulations.
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Parameter values for **yellow** cells:

Cell-cell contact energy: 46
Cell-Collagen I contact energy:(46*2) = **92** for 4-fold change case simulations,
(46*3) = **138** for 9-fold change case simulations,
(46*4) = **184** for 16-fold change case simulations.
Cell-BM (Laminin) contact energy: 4
Cell proliferation: 0.75
MMP diffusion rate: 0.01
MMP-TIMP cooperativity: 2

Supplementary videos

Video S1: Simulation of the evolution of a tumor population with two cell subsets with 4-fold difference in intra-subset cell-cell adhesion and low inter-subset adhesion with low heterogeneity index (HI).

Video S2: Simulation of the evolution of a tumor population with two cell subsets with 4-fold difference in intra-subset cell-cell adhesion and low inter-subset adhesion with high heterogeneity index (HI).

Video S3: Temporal tracking of 3 cells within a tumor population with two cell subsets with 4-fold difference in intra-subset cell-cell adhesion and low inter-subset adhesion with high heterogeneity index (HI), showing migration and cell division events.

Video S4: Simulation of the evolution of a tumor population with two cell subsets with 4-fold difference in intra-subset cell-cell adhesion and high inter-subset adhesion with low heterogeneity index (HI).

Video S5: Simulation of the evolution of a tumor population with two cell subsets with 4-fold difference in intra-subset cell-cell adhesion and high inter-subset adhesion with high heterogeneity index (HI).

Video S6: Simulation of the evolution of a tumor population with two cell subsets with 4-fold difference in intra-subset cell-ECM adhesion with low heterogeneity index (HI).

Video S7: Simulation of the evolution of a tumor population with two cell subsets with 4-fold difference in intra-subset cell-ECM adhesion with high heterogeneity index (HI).

Video acknowledgements: We thank FIJI software developers and MTrackJ plugin developers (Biomedical Imaging Group Rotterdam) that were used to generate the videos of simulations and cells tracking video respectively.