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Optimal collective durotaxis through E-cadherin adhesions

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The directed migration of cellular clusters enables morphogenesis, wound healing, and collective cancer invasion. Gradients of substrate stiffness are known to direct the migration of cellular clusters in a process called collective durotaxis, but underlying mechanisms remain unclear. Durotaxis has been mainly studied when mediated by focal adhesions at the extracellular matrix (ECM) interface. However, in ECM-depleted environments cells migrate through the cell-cell adhesion protein E-cadherin. Here we show that when cell adhesion is mediated by E-Cadherin, clusters of cancer cells dewet on soft substrates and wet on stiff ones. At intermediate stiffness, clusters on uniform-stiffness substrates become maximally motile, and clusters on stiffness gradients exhibit optimal durotaxis. Durotactic velocity increases with cluster size, stiffness gradient, and actomyosin activity. We first demonstrate this new migratory mode on substrates coated with E-cadherin and then establish its generality on substrates coated with extracellular matrix. We develop a physical model of three-dimensional active wetting that explains this mode of collective durotaxis in terms of a balance between in-plane active traction and tissue contractility, and out-of-plane surface tension. Finally, we show that the distribution of cluster displacements has a heavy tail, with infrequent but large cellular hops that contribute to durotactic migration. Our study demonstrates a new physical mechanism of collective durotaxis, through both cell-cell and cell-substrate adhesion ligands, based on the wetting properties of active droplets.