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Spreading and spontaneous motility of multicellular aggregates on soft substrates

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We first describe the biomechanics of multicellular aggregates, a model system for tissues and tumors. We first characterize the tissue mechanical properties (surface tension, elasticity, viscosity) by a new pipette aspiration technique. The aggregate exhibits a viscoelastic response but, unlike an inert fluid, we observe aggregate reinforcement with pressure, which for a narrow range of pressures results in pulsed contractions or shivering. We interpret this reinforcement as a mechanosensitive active response of the acto-myosin cortex. Such an active behavior has previously been found to cause tissue pulsation during dorsal closure of Drosophila embryo. We then describe the spreading of aggregates on rigid glass substrates, varying both intercellular and substrate adhesion. We find both partial and complete wetting regimes. For the dynamics, we find a universal spreading law at short time, analogous to that of a viscoelastic drop. At long time, we observe, for strong substrate adhesion, a precursor film spreading around the aggregate. Depending on aggregate cohesion, this precursor film can be a dense cellular monolayer (liquid state) or consist of individual cells escaping from the aggregate body (gas state). The transition from liquid to gas state appears also to be present in the progression of a tumor from noninvasive to metastatic, known as the epithelial-mesenchymal transition. Finally, we describe the effect of the substrate rigidity on the phase diagram of wetting. On soft gels decorated with fibronectin and strongly cohesive aggregates, we have observed a wetting transition induced by the substrate rigidity: on ultra soft gels, below an elastic modulus Ec the aggregates do not spread, whereas above Ec we observe a precursor film expending with a diffusive law. The diffusion coefficient D(E) present a maximum for E=Em. A maximum of mobility versus the substrate rigidity had also been observed for single cells. Near Em, we observe a new phenomenon: a cell monolayer expands outward from the aggregate apparently under tension. In this tense monolayer, holes nucleate, and lead to a symmetry breaking as the entire aggregate starts to move in a similar fashion as a giant fish keratocyte.