New and Notable

Quantitative Parsing of Cell Multi-tasking in Wound Repair and Tissue Morphogenesis

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Wound healing is a complex process of cell colonization, matrix deposition, and remodeling, requiring multiple cell functions to act in coordinated manner. Focusing on dermal tissue regeneration as a prominent example, a relatively simplified view can be proffered: proper healing requires fibroblast migration into the wound, synthesis and secretion of extracellular matrix components, and active contraction-based reorganization of the matrix around the occupying cells. These actions occur in an overlapping but sequenced order in the face of a multitude of external cues from a changing environment. Further complicating this situation is the fact that these stages of wound repair occur asynchronously across a larger, healing wound. The ways by which these diverse cell behaviors—locomotion, matrix production, and tissue remodeling—interact to ultimately yield either proper tissue physiology or various kinds of pathology remain poorly understood, even to the issue of the nature of the cells involved in any or all of these functions (Tomasek et al., 2002).

For investigators in the biophysics community, an especially germane facet of this complicated phenomenon is the relationship between cell locomotion and matrix reorganization, particularly since the matrix reorganization requires matrix contraction. At their core both the cellular immigration and the matrix contraction arise from intracellular cytoskeletal force generation transmitted to the extracellular matrix via highly regulated cell/matrix adhesion sites (Tamariz and Grinnell, 2002). Controversy has existed in the wound healing and tissue morphogenesis field about whether compaction of extracellular matrix derives, on the one hand, from migrating cells as they exert traction during locomotion, or, on the other hand, by nonmigrating cells converting their intracellular contractile force into traction. In fact, fibroblast motility can be converted into matrix compaction by inhibiting molecular mechanisms involved in regulated release of cell/matrix adhesions operating in migration (Allen et al., 2002). Thus, it is exceedingly difficult to parse contributions of underlying molecular mechanisms to overall wound healing and tissue morphogenesis in terms of active cell migration versus cell motility-derived matrix deformations. It may simply be that they are part-and-parcel aspects of the same underlying motility machinery modulated by external signals that abrogate key events. It is, therefore, crucial to gain this capability for analyzing the ''multitasking'' cells can accomplish with their force generation and transmission regulation in order to test hypotheses that can lead to improved molecular therapeutics for wound regeneration and particularly wound strengthening.

A major advance toward this important goal is provided by the new work by Shreiber et al. in this issue of the *Biophysical Journal* (Shreiber et al., 2003), by simultaneous quantitative measurement of cell migration and matrix deformation for fibroblasts within three-dimensional collagen gels as functions of time over a period of hours. These gels are cylindrical and anchored at their axial ends, so that matrix deformation occurs in the radial direction. The automated microscopy and image analysis technology needed for this capability had been demonstrated previously by the Tranquillo laboratory at Minnesota in recent years, but the crucial extension here determination of time-varying characteristics of these cell behavioral functions concomitantly enabling analysis of dynamic changes in locomotion and remodeling reflecting progressions of the extracellular context (e.g., matrix composition and compliance) as well as cellular phenotypic properties (due to gene expression modulation, for instance).

In this new study, the Tranquillo group compared dynamic cell migration and matrix compaction properties of human foreskin fibroblasts (HFFs) and rat dermal fibroblasts (RDFs) in response to serum. Both cell types generally showed increasing values of the random migration coefficient, μ (analogous to a molecular diffusion coefficient), as time progressed, while the values of the cell traction coefficent, τ_0, exhibited more complex dependence on the experimental time period. Of greatest significance was the behavior found when migration and traction properties were plotted against each other for the full series of time points, revealing striking correlations between traction and migration as both varied during experimental progression. For the HFFs, a strong positive correlation between migration and traction was revealed, suggesting that locomotion of these cells drives matrix deformation. In contrast, for the RDFs, the correlation between migration and traction was primarily negative, indicating that matrix deformation by these cells is diminished when they are more actively locomotory; however, when their traction was low a mild positive correlation with migration was observed. More interestingly yet, the values of the traction coefficient for HFFs fell into a low range (~0.01–0.03 dyne-cm/cell), whereas the values of this force transmission parameter for RDFs spanned across this same range as well as into a much higher level (comprehensively from ~0.01 dyne-cm/cell to ~0.08

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dyne-cm/cell). When Shreiber and colleagues plotted the data for both cell types together, then, a biphasic behavior obtained: in the low-traction regime, migration increased as traction increased, while in the high-traction regime, migration decreased as traction further increased. Thus, under some conditions matrix deformation appears to be associated with cell locomotion, whereas under other conditions matrix deformation appears to be dissociated from cell locomotion. The controversy noted above concerning whether more traction is exerted onto extracellular substrata by cells exhibiting migratory phenotype or by cells exhibiting nonmigratory phenotype may, therefore, be resolved by appreciating that seemingly diverse phenomenological behaviors can be accounted for by quantitative differences in parameter values governing key dynamic balances—in this case, mechanical force balances. This type of situation was predicted theoretically for the relationship between intracellular force generation and cell migration mediated by cell/substratum adhesive interactions (DiMilla et al., 1991), and the Shreiber et al. experimental data are at least consistent with this model prediction. More recently, a superb series of complementary contributions from the collaborative work of Dembo and Wang have provided rigorous quantitative support for the intricate and complex interaction of cell force generation, cell/substratum adhesion, substratum compliance, traction, and cell migration on two-dimensional substrata (Lo et al., 2000; Munevar et al., 2001).

A problem continuing to perplex parsing of the simultaneous relationships of cell force generation to migration and matrix deformation is the confounding interactions of adhesion and traction. It remains very difficult to separate these processes, to measure and/or manipulate one independently of the other. The important advances from the Tranquillo, Dembo, and Wang laboratories in both technical methodologies and conceptual frameworks, however, promises to motivate new efforts to overcome this next challenge in molecular/cell/tissue biophysics.

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