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Review Article

Extracellular Matrix Composition and Retention of Stemness in Cultured Progenitor Cells

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Abstract

Background: Progenitor cells lose potency on tissue-culture plastic, and both substrate mechanics and matrix composition have been proposed as the instruction that preserves it.

Objective: To examine where the mechanical and compositional literatures conflict, and what a substrate specification must state to be reproducible.

Methods: Narrative review of hydrogel differentiation, tethering and defined-substrate culture studies.

Findings: Three osteogenic stiffness windows are reported: 25-40 kPa on two-dimensional collagen-I-coated polyacrylamide, 11-30 kPa in three-dimensional RGD-alginate, and 80 kPa on collagen I alone, with no significant osteogenesis on fibronectin, laminin or collagen IV at any modulus tested. Recombinant laminin-511 supported self-renewal for 20 passages at approximately 97% OCT4-positive.

Conclusions: The evidence supports modulus, dimensionality, coating and relaxation behaviour acting jointly, but not a single stiffness prescription; defined substrates have the stronger record.

Keywords: Extracellular matrix; Substrate stiffness; Stem cell fate; Cell culture substrates; Mesenchymal stromal cells

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Introduction

Progenitor cells lose the properties that make them useful the moment they are put into culture. Human MSCs expanded on tissue-culture plastic showed dramatically diminished skeletogenic capacity after 6-7 passages in an in vivo transplantation assay, whereas the same cells expanded on a reconstituted marrow-derived extracellular matrix retained that capacity over multiple passages [1]. The substrate is not a passive support but an instruction, and the field has spent twenty-five years working out what it says.

The mechanical strand began with fibroblasts on flexible polyacrylamide forming different focal adhesions and moving differently than on rigid glass [2], generalised into the claim that tissue cells feel and respond to substrate stiffness across cell types [3], and reached its most cited form in the report that matrix elasticity alone directs mesenchymal lineage [4]. The biochemical strand replaced undefined feeder layers and Matrigel with defined proteins and peptides supporting long-term self-renewal [5,6,7]. Reviews have tended to present these as complementary [8,9].

They are not straightforwardly complementary. Three studies report three different osteogenic stiffness windows for mesenchymal cells, and the differences are not noise. Engler reports an osteogenic band at 25-40 kPa on two-dimensional collagen-I-coated gels [4]; Huebsch reports osteogenesis predominating at 11-30 kPa for cells encapsulated in three-dimensional RGD-alginate [10]; Rowlands, testing sixteen gel-protein combinations in two dimensions, finds significant osteogenic differentiation only at 80 kPa and only on collagen I, with none on fibronectin, laminin or collagen IV at any modulus tested [11]. A reader looking for the stiffness at which to differentiate osteoblasts will not find one; the window is a joint property of modulus, dimensionality and the protein at the interface.

Three Reported Osteogenic Windows

The Engler values come with a provenance caveat. The published abstract of the Cell paper contains no kPa values; the 0.1-1, 8-17 and 25-40 kPa bands, the 11 and 34 kPa gels, and the 5-, 6- and 4-fold marker changes were read from an author-posted PDF of the manuscript. They are internally consistent, but they are Engler's reported windows rather than publisher-of-record numbers, and nothing below rests on them being more precise than that.

On collagen-I-coated polyacrylamide mimicking brain elasticity, 0.1-1 kPa, naive human MSCs upregulate key neurogenic transcripts by an average of about 5-fold relative to early-passage MSCs. On gels near muscle elasticity, a band given as 8-17 kPa, cells on an 11 kPa gel express 6-fold more myogenic message. On gels said to mimic the crosslinked collagen of osteoid, 25-40 kPa, cells on the stiffest 34 kPa gel express 4-fold more osteogenic message [4]. All of this is two-dimensional culture; replicate numbers are not stated per condition in the accessible text, and the data are given as means with standard errors. Inhibiting non-muscle myosin II with blebbistatin suppresses this elasticity-directed expression roughly 10-fold on Western blots, placing contractility upstream of the readout.

Huebsch encapsulated MSCs in three-dimensional RGD-coupled alginate and found osteogenesis predominant over 11-30 kPa [10]. Replicate numbers are not stated in the accessible abstract. The band is both lower and narrower than Engler's, and the two overlap only across 25-30 kPa. A gel at 15 kPa is osteogenic in Huebsch's three-dimensional system and myogenic in Engler's two-dimensional one.

Rowlands is the more disruptive result. Human MSCs were cultured on polyacrylamide gels covalently coated with collagen I, collagen IV, laminin or fibronectin across a modulus series, sixteen gel-protein combinations in two dimensions. Osteogenic differentiation occurred

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significantly only on collagen-I-coated gels at the highest modulus tested, 80 kPa [11]. Replicate counts are not given in the accessible abstract. First, 80 kPa lies entirely outside both other windows. Second, on three of the four coatings there was no osteogenic window at all across the range tested. Stiffness by itself did not produce osteoblasts.

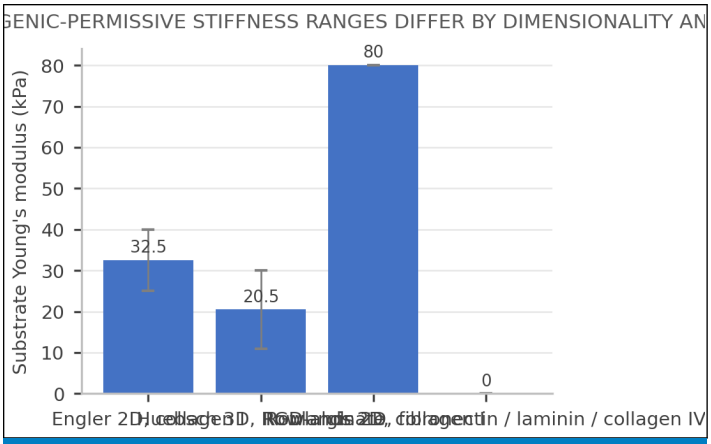

Figure 1: The three reported osteogenic stiffness ranges do not overlap and depend on dimensionality and coating - 25-40 kPa on 2D collagen-I polyacrylamide [4], 11-30 kPa in 3D RGD-alginate [10], and 80 kPa on 2D collagen I only, with no significant osteogenesis on fibronectin, laminin or collagen IV at any modulus among the 16 gel-protein combinations tested [11]; N per condition is not reported in the accessible sources.

Coating Protein as an Independent Variable

The same study makes the coating dependence quantitative in the myogenic channel. Myogenic differentiation occurred on every gel-protein combination stiffer than 9 kPa, but to varying extents by MyoD1 expression, with peak MyoD1 on 25 kPa fibronectin-coated gels and comparable levels on 80 kPa collagen-I gels [11]. A 25 kPa fibronectin gel is therefore maximally myogenic in Rowlands' hands while sitting inside the band Engler assigns to osteogenesis. Ligand identity does work a single elasticity axis cannot represent.

Rowlands also reports that stiffer substrates supported up to a 10-fold increase in cell number relative to softer gels [11]. Proliferation and differentiation therefore scale together with modulus, complicating any reading of marker expression per culture as a per-cell fate decision.

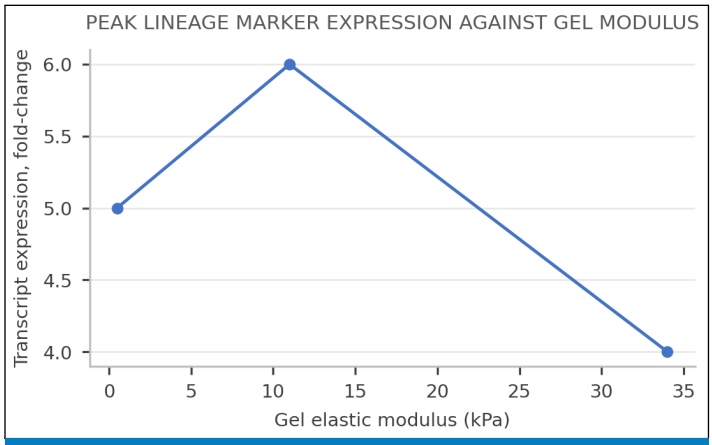

Figure 2: Peak neurogenic, myogenic and osteogenic transcript levels reported for human MSCs on 2D collagen-I-coated polyacrylamide, plotted as three separate marker panels rather than one dose-response, at 0.5 kPa (5-fold), 11 kPa (6-fold) and 34 kPa (4-fold) [4]; N per condition is not stated in the accessible source, data reported as mean +/- SEM.

Compliance and ligand density were separated experimentally in cell-on-gel responses before the lineage work [12], and matrix composition instructing stem cell fate is the framing of the field's reviews [8]. What Rowlands adds is that composition can abolish a stiffness effect entirely rather than merely scaling it.

Collagen I, collagen IV, laminin and fibronectin are ligands for different integrin heterodimers, present different numbers and spacings of binding motifs on polyacrylamide, and differ in their own compliance as a layer between cell and gel. Rowlands held the gel and coupling chemistry constant across all sixteen combinations and varied only protein and modulus, so the divergence is attributable to the ligand, not to gel preparation differing between laboratories. That is the strongest available evidence that the osteogenic window is not a property of the gel. Comparisons across studies that also differ in polymer, coupling and cell source cannot make the same claim, and much of the apparent consensus in the secondary literature is assembled from them.

Dimensionality Changes What the Cell Is Measuring

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Cell-matrix adhesions in three dimensions differ in composition, structure and signalling from focal adhesions on two-dimensional substrates [13], so a modulus measured on a flat gel need not mean the same thing to a cell inside a network, which must also deform or degrade its surroundings to spread. Khetan showed in covalently crosslinked three-dimensional hydrogels that it is degradation-permitted cellular traction, not stiffness, that selects lineage: restricting degradation shifted MSC fate independently of the bulk modulus [14]. Huebsch's three-dimensional window is best read as a range over which traction at the cell-matrix interface is productive rather than as an intrinsic mechanical setpoint.

The molecular-clutch account explains why the mapping between modulus and response need not be monotonic or transferable: force transmission through adhesions depends on the loading rate of the clutch, producing a rigidity threshold rather than a smooth gradient, and the position of that threshold depends on adhesion and actin parameters as much as on the substrate [15]. Different coatings engage different integrins with different clutch parameters, so the model predicts a coating-dependent window.

Elasticity Is Not the Only Mechanical Variable

Two further findings undercut the idea that a gel is fully described by its Young's modulus. Trappmann reported that on substrates spanning 0.1 kPa to 2.3 MPa, cells on 0.5 kPa polyacrylamide could not form stable adhesion structures, and that lowering collagen anchoring density altered differentiation at constant stiffness, arguing that cells sense the tethering of matrix protein rather than bulk elasticity [16]. Wen found that increasing protein-substrate linker density up to 50-fold changed tethering but did not affect osteogenesis, adipogenesis, surface-protein unfolding or substrate deformation [17]. This second disagreement, unresolved, bears directly on the first: if coupling chemistry can change the outcome at fixed modulus, then two laboratories reporting different windows may be reporting different interfaces.

Table 1: Variables other than Young's modulus that alter progenitor cell outcome, with the condition and culture dimensionality as reported; replicate numbers are not stated in the accessible sources [16,17,19,23,24,25].

Variable	Reported condition	Format	Reported effect
Protein tethering	0.1 kPa-2.3 MPa; no stable adhesions at 0.5 kPa	2D	Anchoring density shifts fate at fixed stiffness
Protein tethering	Linker density raised up to 50-fold	2D	No effect on osteogenesis or adipogenesis
Stress relaxation	17 kPa initial modulus, fast-relaxing gel	3D	Mineralised, collagen-1-rich matrix formed
Culture history	Stiff surface, then 2 kPa PEG hydrogel	2D	YAP/TAZ and RUNX2 activation persists
Cell-intrinsic stiffness	Differentiated cells ~10x stiffer than mESC	2D	Stress spreads soft cells, lowers Oct3/4
Substrate for self-renewal	12 kPa gel versus ~10^6 kPa plastic	2D	MuSC self-renew and regenerate after transplant

Viscoelasticity is the other omitted variable. Alginate gels can be tuned to relax stress faster or slower at matched initial modulus, and cells spread more on stress-relaxing substrates than on purely elastic ones of the same initial stiffness [18]. In rapidly relaxing hydrogels with an initial elastic modulus of 17 kPa, MSCs formed a mineralised, collagen-1-rich matrix resembling bone, with spreading, proliferation and osteogenic differentiation all enhanced relative to slower-relaxing gels of the same initial modulus [19]. Half-relaxation times separating fast from slow gels could not be confirmed from an accessible source; the qualitative comparison stands without them. The case that viscoelasticity is a distinct instructive parameter has since been made systematically [20]. 17 kPa sits inside Huebsch's band and below Engler's, and at that modulus the osteogenic outcome is set by relaxation rate.

Nor is the substrate's instantaneous state sufficient. YAP and TAZ transduce mechanical cues to the nucleus and

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are required for the substrate-dependent behaviour of mesenchymal cells [21,22], and their activation carries history: cells cultured on stiff surfaces before transfer to 2 kPa poly(ethylene glycol) hydrogels retain YAP/TAZ and RUNX2 activation in proportion to prior time on the stiff surface, and past a threshold mechanical dose the activation becomes irreversible [23]. Cells arriving from roughly 3 GPa polystyrene are not mechanically naive. The cell's own material properties matter too: differentiated cells are about tenfold stiffer than undifferentiated mouse embryonic stem cells, and applied stress spreads the soft undifferentiated cells while downregulating Oct3/4 [24].

Where self-renewal rather than differentiation is the goal, the elasticity result is cleaner. Muscle stem cells on rigid plastic, approximately 10^6 kPa, lose regenerative capacity, whereas the same cells on 12 kPa hydrogels matching muscle elasticity self-renew in culture and contribute extensively to regeneration after transplantation [25]. Retention of stemness and induction of a lineage are different problems with different substrate requirements. Gilbert's 12 kPa is a self-renewal condition for a committed adult stem cell in two dimensions, and should not be read onto the osteogenic axis, even though it falls inside Huebsch's three-dimensional band and just below Engler's myogenic gel. Table 1 collects these non-modulus variables with the conditions and dimensionality as reported.

Composition-Defined Substrates and Retained Potency

The compositional literature has produced more transferable results, because it specifies what the cell binds rather than only how hard the surface is. Recombinant laminin-511 supported human ES and iPS cell self-renewal with normal karyotype for at least 4 months, 20 passages, with clump-plated hES cells approximately 97% OCT4-positive [6]. Laminin-521 combined with E-cadherin permitted clonal culture without ROCK inhibitor at about 20% cloning efficiency in two lines, with three lines carried 37, 25 and 35 passages over 12, 8 and 11 months [26]. Laminin E8 fragments maintained three hESC and two hiPSC lines for 10 passages, and 30 passages with normal karyotype, with adhesion greater than on Matrigel or intact laminin isoforms [27]. Synthetic peptide-acrylate surfaces carried H1 and H7 hESC beyond 10 passages with phenotype comparable to Matrigel [7], and recombinant vitronectin supports self-renewal through alpha-v-beta-5 integrin [28] in fully defined systems [29].

Table 2: Coating and format against reported proliferation and potency outcomes for mesenchymal and pluripotent cells [11,10,1,6].

Coating	Format	Proliferation	Lineage or potency
Collagen I	2D gel	Up to 10x more cells on stiff gels	Osteogenic only at 80 kPa
Fibronectin	2D gel	Rises with modulus	No osteogenesis; MyoD1 peak 25 kPa
Laminin	2D gel	Rises with modulus	No osteogenesis at any modulus
Collagen IV	2D gel	Rises with modulus	No osteogenesis at any modulus
RGD-alginate	3D gel	Not reported	Osteogenic at 11-30 kPa
Marrow ECM	2D	Promoted, no value given	Potency held past passage 6-7
Laminin-511	2D	Not reported	20 passages, 97% OCT4+

For mesenchymal cells the equivalent is cell-derived matrix. Marrow cell-derived ECM contains collagens I and III, fibronectin, biglycan, decorin, perlecan and laminin [1], with collagen V and the same basement membrane components reported independently [30]; expansion on such matrices preserves potency past the passage at which plastic-expanded cells fail [1]. Tightly anchored tissue-mimetic matrices reproduce this in a defined format [31], and decellularized matrix models sustain viability consistently above 98% live cells at day 5 with n = 6, with a stemness gene panel at n = 4-10 [32]. In that model the Oct4 upregulation in the three-dimensional bone-derived matrix relative to control did not reach

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significance, at p = 0.0651. The field's reviews treat cell-derived matrix as a compositional rather than mechanical intervention [9], and its attraction is that such a matrix supplies collagen, proteoglycan and basement membrane components together, arranged as the cells that deposited it selected, without the investigator knowing which component carries the instruction. The cost is that composition is only partly specified and batch variation is hard to control, the same objection that motivated the move away from Matrigel toward single recombinant proteins in pluripotent culture [5].

Conclusion

The three osteogenic windows should be reported as three findings, not averaged into one. Engler's 25-40 kPa applies to two-dimensional collagen-I-coated polyacrylamide; Huebsch's 11-30 kPa to three-dimensional RGD-alginate; Rowlands' 80 kPa to two-dimensional collagen I alone, with fibronectin, laminin and collagen IV yielding nothing across the range. Together they say that a stiffness prescription is meaningless without its dimensionality and its coating, and that on three of four common coatings there may be no osteogenic window at all. Tethering chemistry [16,17], stress relaxation [19], degradability [14] and culture history [23] each move the outcome at fixed modulus. For retention of stemness rather than directed differentiation, the compositionally defined substrates have the stronger record, because they state what is present. A useful methods section names the coating protein, its coupling chemistry, the dimensionality, the relaxation behaviour and the culture history, and reports the modulus as one parameter among them rather than as the condition itself.

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