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COMP-lex mechanics: Matricrine signaling

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Emerging evidence continues to support the functional importance of extracellular matrix (ECM) proteins in cellular signaling. In mineralizing tissues, including bone, cartilage and vasculature, ECM proteins not only provide the microenvironment for propagation of crystal growth but also support and transmit mechanical cues to the cells, and these cues govern many aspects of cell function, including proliferation and differentiation. When cells interact with the matrix and produce their own matrix proteins, it is a form of intercellular communication. Although this “matricrine” signaling receives less research attention than chemical forms of intercellular communication, such as autocrine and paracrine signaling, it is important in biomineralization in both health and disease.

In this issue of *Circulation Research*, Fu and colleagues¹ highlight the important role of the non-collagenous ECM protein, cartilage oligomeric matrix protein (COMP) in calcific atherosclerosis. COMP, a member of the thrombospondin family of proteins (TSP-5), maintains cartilage structural integrity by binding collagen and other ECM proteins, such as aggrecan (chondroitin sulfate proteoglycan 1), aggregates of which give cartilage its springy resistance to compression.^{2–4} COMP overexpression enhances ECM organization and assembly by increasing total soluble glycosaminoglycan content and levels of aggrecan and

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collagen type II.⁵ Thus, COMP appears to control the assembly and maintenance of the tertiary architecture of extracellular matrix. Its homopentameric structure, like that of a spiny starfish, allows it to bind to multiple sites, bridging collagen fibrils to one another and bridging cells to matrix proteins and proteoglycans.⁶

ECM proteins interact with the intracellular cytoskeleton through mechanical links with integrins. As described elegantly by Ingber and colleagues, as a tensegrity model, the mechanical features of ECM are central determinants of cell shape⁷ and, thus, cell behavior. One robust example of the ability of ECM mechanical characteristics to control cell behavior consists of lineage determination. For instance, Simmons and colleagues showed that valvular cells undergo osteochondrogenic differentiation when grown on an ECM with a particular range of elastic modulus (25–30 kPa), whereas on a less compliant matrix (110 kPa), valvular cells undergo myofibroblastic differentiation.⁸ Similarly, the Anseth group showed that growth on a substrate with lower elastic modulus directs valvular myofibroblasts into a more dormant fibroblastic phenotype.⁹

One possible mechanism, by which matrix stiffness may control cell differentiation is through release of morphogens from sites on binding proteins that bridge cellular integrins with ECM proteins, as proposed by Hinz.¹⁰ In this paradigm (Figure 1), transforming growth factor- β (TGF- β) superfamily members, which include molecular morphogens, are held in, what we term, “spring-loaded” sites in latent binding proteins that are strategically located between integrins and anchored ECM proteins. Even a brief contraction of the cytoskeleton may allow a cell to “sense” local ECM properties by tugging on the chain of proteins (integrins/binding proteins/ECM proteins). If the cell tugs on a stiff ECM, the resistance produces tension that can unfold a binding protein “spring” to release the morphogens, which may then activate receptors on the cell surface. However, if the cell tugs on a compliant ECM, the matrix may simply “give,” offering no resistance, generating no tension to open the binding protein, and failing to release the morphogen.¹¹ This concept of a “spring-loaded morphogen” is attractive since it may account for the many known effects of matrix elasticity on cellular differentiation.

Canfield and colleagues first described the presence of COMP in calcific atherosclerosis in 1998.¹² They demonstrated that COMP is present in the fibrous tissue and in areas of microscopic calcium deposits in atherosclerotic lesions.^{12, 13} More recently, Du and colleagues showed that COMP deficiency markedly exacerbates – and its ectopic expression greatly reduces – vascular calcification. These findings suggest that it has a compensatory, negative feedback role.¹⁴ In vascular cells, COMP is also interacts with integrins, a key participant in matricrine signaling.¹⁵ One may speculate, based on the function of COMP in cartilage tissue, that it acts as a tertiary mechanical bridge in ECM, providing greater strength and greater resistance to stretch. If so, then a substrate deficient in COMP may be more compliant (a lower elastic modulus), which is associated with osteochondrogenic differentiation. Conversely, it is conceivable that, if COMP were overexpressed in valvular cells, valve stiffness would increase and direct the cells to a myofibroblastic lineage, which may lead to scar-like contracture and retraction, as seen in human aortic stenosis.

Recent evidence raises the possibility that COMP may be involved in a spring-loaded-morphogen mechanism, given its binding to integrins, its binding to the morphogen, bone morphogenetic protein-2, and its involvement in presenting such factors to cell surface receptors. Similar to the findings by Fu and colleagues in this issue of *Circulation Research*,¹ Di Cesare and colleagues showed that COMP interacts with cells via the integrin receptor, alpha 5 beta 1.⁶ Interestingly, given that Du et al. showed that COMP binds to BMP-2,¹⁴ an alternative mechanical phenomenon may take place (Figure 2). In this alternative model, mechanical tension may alter the ability of COMP to present BMP-2 to its cell surface receptor. When a cell contracts on a more flexible (compliant) substrate, COMP may be free to present BMP-2 to the cell. In contrast, on a rigid substrate, COMP may be held back or stretched into an elongated configuration that does not allow ligand presentation. This conjecture is supported by the finding that COMP overexpression alters sensitivity of C3H10T1/2 mesenchymal cells to BMP-2.¹⁶

Fu and colleagues¹ also provide strong support for earlier findings, highlighting the role of inflammation in atherosclerotic calcification. The authors demonstrate that bone marrow-derived inflammatory cells are increased in the circulation of COMP-deficient hyperlipidemic mice. Inflammation, which has long been associated epidemiologically with increased risk of cardiovascular mortality,^{17, 18} precedes vascular matrix calcification, and inflammatory cells, specifically monocyte-macrophages, are found in close proximity to calcific atherosclerotic lesions.¹⁹ Inflammation also has substantial effects on matrix remodeling, promoting degradation by metalloproteinase induction and promoting new matrix by increasing expression and synthesis of certain ECM proteins. Li and colleagues showed that production of metalloproteinases by activated macrophages may increase plaque vulnerability by destabilizing calcified nodules.²⁰

Inflammation is also associated with cellular mechanisms of cardiovascular disease. Fu and colleagues highlight the important contributions and additive effects of mesenchymal and hematopoietic lineage cells in calcific vasculopathy.¹ Their findings are in agreement with previous lineage tracing studies showing that both VSMC and marrow-derived cells contribute to biomineralization in atherosclerotic lesions.²¹ Direct effects of activated monocyte/macrophages on vascular cell calcification were first described in 2000 through the potent pro-osteochondrogenic cytokine, TNF- α .^{22, 23} In hyperlipidemic mice, TNF- α is expressed locally in valvular leaflets, where calcified nodules occur.²⁴ In definitive studies tying these concepts together, the Towler laboratory showed that TNF- α neutralizing antibodies (infliximab) reduced aortic calcium accumulation and osteochondrogenic differentiation of aortic myofibroblastic cells in a mouse model of calcific atherosclerosis.²⁵

In the past, autocrine and paracrine molecular signaling mechanisms have been considered the primary means by which cells share information in inflammation. The findings by Fu and colleagues¹ support the importance of matricrine signaling, a less appreciated mechanism of intercellular communication, but an important additional layer of control for cellular behavior and differentiation.

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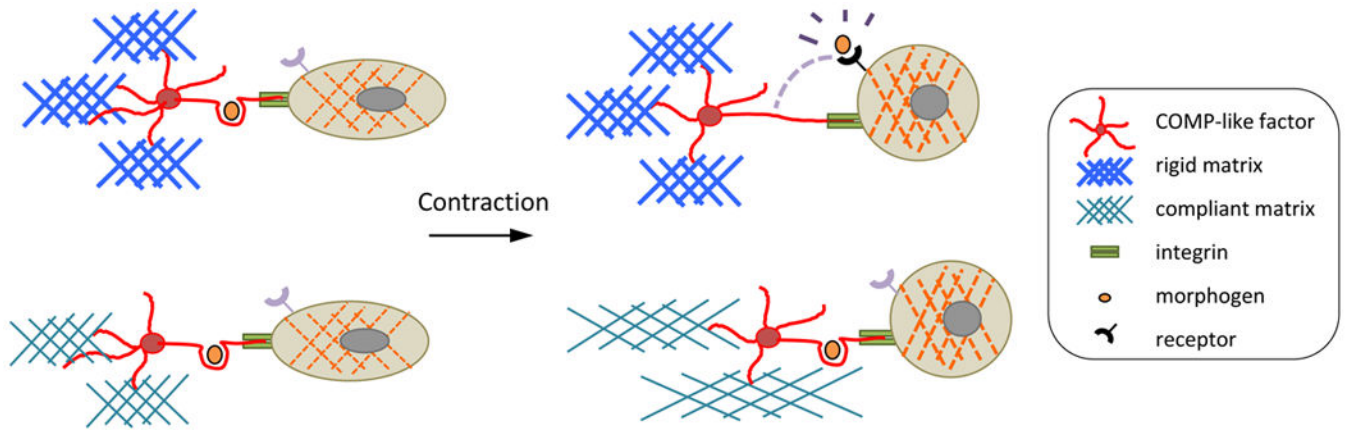


Figure 1. Speculative model of “spring-loaded morphogen” release

Based on the mechanism proposed by Hinz,¹⁰ this schematic shows that binding of cells via integrins to extracellular matrix proteins, such as collagen and homopentameric COMP, allows cells to detect substrate stiffness, by a brief cytoskeletal contraction that releases growth factors or morphogens. When the ECM is altered by inflammation, proteases, mechanical injury, and/or contraction of neighboring cells, cells may detect it by receptor activation by molecular factors upon contraction. Iterative feedback loops may arise if these factors induce synthesis of new matrix, which may change matrix stiffness and/or sensitivity to inflammatory factors.

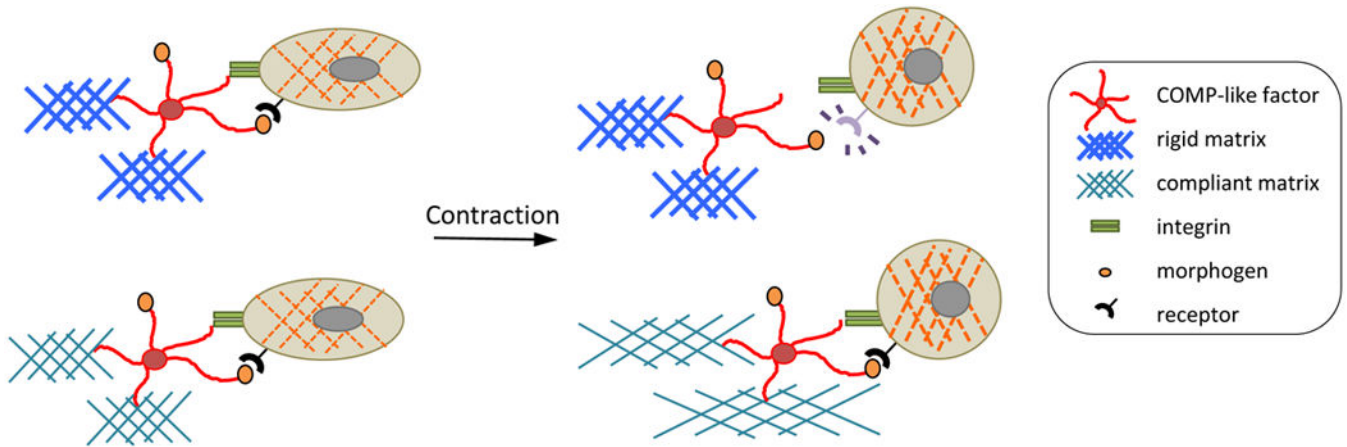


Figure 2. Speculative model of “tethered morphogen” release

In this model, based on the findings by Fu et al,¹ Di Cesare et al,⁶ and Du et al,¹⁴ mechanical tension may alter the ability of COMP to present a morphogen, such as BMP-2, to its cell surface receptor. On a more flexible (compliant) substrate, COMP may be free to present BMP-2 to the cell. In contrast, if the cell contracts on a rigid substrate, ligand presentation by COMP may be lost. While this phenomenon would have the opposite effect on morphogen binding as the spring-loaded paradigm, both phenomena would allow cells to convert mechanical to chemical signals in order to “sense” matrix stiffness.