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Tumor-induced solid stress activates β-catenin signaling to drive malignant behavior in normal, tumor-adjacent cells

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Abstract

Recent work by Fernández-Sánchez and coworkers examining the impact of applied pressure on the malignant phenotype of murine colon tissue in vivo revealed that mechanical perturbations can drive malignant behavior in genetically normal cells. Their findings build upon an existing understanding of how the mechanical cues experienced by cells within a tissue become progressively modified as the tissue transforms. Using magnetically stimulated ultra-magnetic liposomes to mimic tumor growth -induced solid stress, Fernández-Sánchez and coworkers were able to stimulate β-catenin to promote the cancerous behavior of both a normal and genetically modified colon epithelium. In this perspective, we discuss their findings in the context of what is currently known regarding the role of the mechanical landscape in cancer progression and β-catenin as a mechanotransducer. We review data that suggest that mechanically regulated activation of β-catenin fosters development of a malignant phenotype in tissue and predict that mechanical cues may contribute to tumor heterogeneity.

Keywords

β-catenin; colon cancer; mechanobiology; tumorigenesis

Introduction

Tumorigenesis is a multifaceted process initiated by genetic modifications and mediated by biochemical and biophysical cues from the tissue microenvironment. Recent findings highlight the emerging role of cell and tissue context as a key regulator of tumor behavior and stress the importance of the mechanical microenvironment as a modifier of the malignant phenotype [1]. In particular, the mechanical context-oriented paradigm postulates that interactions between tumor cells and normal cells and tumor cells and their extracellular matrix (ECM) create a dynamic mechanical relationship that fosters the malignant phenotype of the genetically transformed tissue. The “mechano-context” prediction maintains that while the malignant potential is dictated by the intrinsic genetic state of the cells, the tumor phenotype is regulated by an evolving balance between the physical and biochemical properties of the cellular constituents and the ECM, which synergistically alters

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cellular behavior by engaging actomyosin-contractility and stimulating migration, invasion, proliferation, and survival. The “mechano-thesis” of cancer implies that as a tumor develops, the increasing disorganized cell mass elevates the solid stresses experienced by both genetically transformed cells and their neighboring normal cells and that these stresses actively participate in driving aberrant tissue behavior [2]. In addition to increases in solid stress, malignant transformation is also associated with matrix metalloproteinase (MMP)-mediated ECM remodeling and altered matrix deposition and crosslinking, driving ECM stiffening [3]. The rich chemokine and cytokine milieu of the tumor, together with the stiffer ECM, stimulate neovascularization and eventually compromise vascular integrity, which, when combined with the increased tumor mass and impaired lymphatic clearance, can elevate interstitial fluid pressure in the tumor tissue as much as 10-fold [4–6]. Thus, during tumor development, both the normal and genetically transformed cells within the tissue are exposed to a complex, interwoven, and continuously evolving mechanical landscape that is highly heterogeneous. Due to the complexity of mechanical cues tumor cells can experience in vivo, the vast majority of studies have been executed using isolated cell lines with defined, in vitro systems where compression, flow, and ECM stiffness can be precisely controlled. Meanwhile, the results obtained from those few studies that have attempted to manipulate the mechanical milieu in vivo, while provocative, have been unable to generate a definitive conclusion regarding the specific contribution of ECM stiffness, flow, or compression on a specific tumor behavior. In this article, we review a recent publication by Fernández-Sánchez et al., which for the first time makes a strong case for how mechanical cues, in this case compressive force, can drive the malignant behavior of normal and genetically primed colon epithelium by activating β-catenin. We discuss these findings in the context of prior experimental data that have similarly implicated β-catenin as a key, mechanically activated pathway critical for expression of the malignant phenotype. We pose critical questions raised by these findings, including whether increasing our understanding of how mechanical stimuli modifies cell signaling could elucidate drivers of tumor heterogeneity and therapy resistance, inform diagnosis, and guide the development of new treatment strategies.

Cancer progression is associated with changes in tissue mechanics

Native tissue undergoes a variety of architectural and mechanical changes following cancer initiation and coincident with tumor progression. These changes alter the mechanical stimuli experienced by cells within the tissue, including solid stresses, or stresses exerted by solid components of the tissue, and hydrostatic and osmotic pressure, and intrinsic mechanical properties of the tissue [1, 7]. Within the primary tumor, the increase in cell mass due to deregulated proliferation and apoptosis exerts solid stress on neighboring, non-malignant cells and adjacent tissue [7, 8]. In turn, the tumor itself experiences compressive forces derived from resistance to its growth and volumetric expansion from the surrounding tissue [7, 8]. Simultaneously, the tumor mass deforms lymphatic and blood vessels, which, combined with the evolving mass, elevates interstitial fluid pressure [7, 9, 10]. Preceding and concurrent with these altered stresses, increased ECM deposition and remodeling modifies the topography, density, and mechanical properties of the ECM, further increasing both solid and fluid stresses [3, 11]. Indeed, mechanical changes associated with malignancy

occur in tandem and can often exacerbate one another [7, 12]. Increased density of ECM molecules, for example, can stiffen the ECM and provide obstruction to interstitial flow, thereby increasing interstitial fluid pressure. Observations of such extensive mechanical changes in tumor tissue have led researchers to ask the obvious question: are these biophysical changes merely passengers in tumor progression? Or do these changes actively promote tumor development and progression?

A variety of both in vitro and in vivo mechanical manipulations have demonstrated that altered mechanical cues can modify cell signaling to elevate growth, promote migration and invasion, and enhance cell survival – all features associated with a malignant phenotype. Compressing cancer cells activates ECM deposition and enhance integrin adhesion strength to induce invasion and promote migration [13]. Additionally, compression of the tumor-resident vessels during tumor growth creates a hypoxic environment within the tumor that hinders tumor-suppressive immune cell function while indirectly driving pro-tumorigenic signaling in cancer cells [9, 14, 15]. Elevated interstitial flow and shear stress alter gene expression, activate architectural changes in the tumor ECM, and can even direct tumor invasion [16, 17]. Similarly, stiffening the ECM can alter cell-matrix adhesion to stimulate the directed migration of pancreatic, brain, prostate cancer cells [18–20]. The relevance of these mechanically induced changes in tumor behavior was illustrated by studies in pancreatic cancer, where decreasing interstitial fluid pressure or solid stresses enhanced chemotherapeutic effectiveness to improve mouse survival [21–23]. Similarly, mitigation of ECM stiffening or tempering integrin-linked mechanosignaling delayed tumor development, reduced cancer incidence, and prevented metastasis [24, 25].

Tumor-associated solid stress induces malignant behavior in non-transformed, tumor-adjacent cells in a colon cancer model

In vitro studies have afforded researchers the ability to hone in on how mechanical cues regulate cell behavior. Recapitulating the same level of precise measurement and manipulation in vivo, however, has posed a greater challenge. Not only do many factors contribute to the mechanical environment in vivo, they are often interrelated, making it difficult to characterize the specific contribution from or to independently perturb only one of these parameters. Increasing matrix crosslinking, for example, not only changes the stiffness of the ECM, but can also decrease pore size and impede blood vessel integrity to increase interstitial fluid pressure [26]. Fernández-Sánchez and coworkers directly applied solid stress to murine colon tissue in vivo and demonstrated that prolonged exposure to elevated solid stress enhanced proliferation of and induced malignant behavior in non-transformed, tumor-adjacent cells by activating β-catenin-mediated transcript of gene targets that have been implicated in malignancy [27]. In their studies, the authors first characterized strain deformation in colon cancer in a widely used Apc model to demonstrate that tumorous colon crypts are characterized by increased levels of solid stress associated with tumor growth and elevated tumor mass (Fig. 1A). They then designed a rigorous approach to replicate these solid stresses using a combination of intravenously injected ultra-magnetic liposomes and a subcutaneously inserted magnet. By applying a magnetic field gradient, they were able to replicate solid stresses comparable to those measured in their experimental

model of oncogene-induced colon cancer (Fig. 1B). The authors then observed sustained activation of β-catenin signaling in tumor-adjacent cells, evidenced by nuclear translocation of β-catenin, transcription of β-catenin targets, and elevated proliferation and crypt growth (Fig. 1C). Importantly, the authors concluded that mechanical induction of malignant behavior in normal tissue adjacent to the tumor did not depend upon the presence of prior genetic abnormalities. The findings therefore argue that the cancerous behavior of a tumor may be propagated via a positive feedback loop in which mechanical pressure from the primary tumor induces tumorigenic signaling in non-transformed, adjacent cell populations, which could in turn drive cell growth and increases in tumor growth-associated solid stress.

The article by Fernández-Sánchez and coworkers represents a strong addition to the emerging consensus that changes to the mechanical environment intrinsic to cancerous tissues can and does directly modify the behavior of cells within the tissue, even in genetically normal cells. The work also provides a plausible explanation for the emergence of tumor heterogeneity and raises the possibility that such insight could be useful for developing new strategies to identify and treat cancer. Perhaps the most intriguing advance made by Fernández-Sánchez et al. is their defined method of increasing solid stress in a tissue without altering ECM stiffness. The employment of ultra-magnetic liposomes represents a low impact perturbation that could be a useful approach with which to precisely modulate the mechanical microenvironment. Using this technique to make a direct functional link between a mechanical perturbation and cell fate changes signals a new era of mechanobiology, where novel technologies enable the field to answer questions that were previously veiled by technical hurdles (Fig. 2).

Mechanotransduction promotes cancer progression

While the connection between increased solid stress or tumor stiffness and cancer progression is now slowly gaining credence, identifying the molecular mechanisms whereby altered tissue mechanics can foster the malignant behavior of a tissue has proven more elusive. Nevertheless, a succession of recent studies has shed light on important regulators linking mechanotransduction to cell growth, proliferation, migration, and apoptosis resistance. For example, integrin clustering, adhesion plaque formation, and cytoskeletal remodeling have been consistently identified as key mechanisms via which a cell responds to a stiffened ECM [24, 28]. Activation of focal adhesion proteins such as focal adhesion kinase (FAK) and Src transduce integrin activation to canonical growth and survival signaling pathways, including Ras/MAPK, Akt, and Rac [29, 30]. Presumably, additional molecular pathways will be identified as research interest in this emerging field grows.

A question of particular interest to researchers has been whether altered tissue mechanics is merely a byproduct of malignant progression or whether it can independently modify and/or accelerate cancer progression and aggression. To that end, multiple studies have highlighted the role of mechanical cues in promoting tumorigenic behavior in non-transformed cell populations and in fostering or restricting the malignant transformation of an oncogenically primed tissue. Work conducted using established human mammary epithelial cells (MECs) and mouse mammary tumor models showed that ECM stiffening sensitizes normal cells to growth factor cues [28, 31], drives pro-growth and proliferation signaling [10, 24, 28, 32],

and increases tumor incidence and metastasis [24, 33]. Li and Hanahan [34] further support these findings by implicating the NMDAR signaling circuit as a mediator of interstitial fluid pressure-driven malignancy in a murine model of pancreatic neuroendocrine tumorigenesis. Recent studies have begun identifying specific molecular mechanisms that link mechanical perturbations to tumori-genesis. Mouw et al. [32] highlighted the importance of integrin-FAK driven β-catenin signaling in stiffness-mediated breast cancer progression and the currently discussed article directly builds upon these findings, particularly with respect to implicating β-catenin signaling in mechanotransduction and induction of the malignant phenotype. By contrast, there has been significantly less work addressing the impact of solid stress and interstitial fluid pressure on tumor cell behavior. Hints from stiffness-related studies certainly suggest that mechanical inputs can have tumorigenic effects, and the results from Fernández-Sánchez and coworkers will hopefully inspire further studies in other model systems.

β-Catenin signaling has emerged as an important component of both mechanotransduction and tumorigenesis

Compared to ion channel activation and integrin-induced signaling through Rho-associated protein kinase (ROCK), Wnt and β-catenin are relative newcomers to the club of mechanotransducers. Canonically, Wnt/β-catenin signaling regulates cell polarity, proliferation, and differentiation during embryogenesis [35]. Wnt proteins are secreted morphogens that elicit their effects by stimulating the receptors Frizzled and LDL receptor-related proteins 5 and 6 (LRP5 and LRP6) to activate β-catenin [35]. In the absence of ligand-induced activation, β-catenin is phosphorylated and directed for ubiquitin-mediated degradation by the Axin complex, a process controlled by interactions with GSK3, CK1α, and APC [35, 36]. Wnt receptor disrupts the Axin complex, thereby inhibiting β-catenin phosphorylation [35]. The newly stabilized β-catenin is no longer sent for degradation and is found to be transported at higher rates to the nucleus, where it can activate transcription of downstream targets involved in proliferation and fate specification during development [37]. In recent years, β-catenin has been strongly implicated as a mechanically activated regulator of embryogenesis, where, in response to mechanical strain, β-catenin translocates to the nucleus to turn on genes that direct mesoderm specification [38]. Similarly, mechanical loading in bone increases the Wnt expression and Wnt/β-catenin activation critical for bone development [39]. Exposure to cyclic hydrostatic pressure also reduces the association of β-catenin to N-cadherin at the cell membrane to allow its nuclear localization [40].

Genetic evidence through loss and gain of function studies definitively support a central role for β-catenin in development, and biophysical manipulations have implicated tissue mechanics as a key regulator of β-catenin activation during cell fate determination [38, 40–42]. Similarly, genetic evidence has linked abnormal β-catenin activation to malignancy; a recent study by Dow and coworkers [43] illustrated its essential role in driving expression of the malignant phenotype. However, only recently have new data emerged in support of a role for mechanical activation of β-catenin as a regulator of cancer. In a series of studies using a carcinogen-induced mouse model of squamous carcinoma and genetically engineered mouse models, Samuel et al. [25] showed that ECM stiffness and actomyosin-

mediated cellular tensionare essential for ROCK2-dependent, β-catenin-mediated hyperplasia and malignancy. Additionally, Mouw et al. [32] demonstrated that ECM stiffness and elevated integrin-dependent FAK activation foster malignant transformation and metastasis of mammary tumors by chronically stimulating β-catenin. These results are consistent with prior work by Whitehead et al. [44] that implicated mechanical compression of colon crypts to increased nuclear localization of β-catenin in vitro. The work reported by Fernández-Sánchez et al. thus contributes to the emerging link between mechanical inputs and β-catenin-mediated mechanosensing and the malignant phenotype. Their work is particularly significant because of the defined use of mechanical stimulation to drive the malignant behavior of non-malignant cells within a tissue. Their findings effectively demonstrate for the first time, in vivo, that mechanical stimuli can drive expression of the malignant phenotype, and suggest that β-catenin transduction of local perturbations in the mechanical landscape may be one important mechanism contributing to the aberrant signaling characteristic of tumor heterogeneity.

Conclusions

Tumorigenesis is a complex process governed by many factors, including genetic modifications and altered biochemical and mechanical cues. Here, we discussed a provocative article that features the precise in vivo manipulation of solid stress and studies that functionally link aberrantly elevated solid stress to the malignant behavior of a tissue. The article distinguishes itself in that it is the first case to definitively demonstrate how tumor-induced solid stress, per se, may be sufficient to activate a key signaling pathway (β-catenin) that has previously been strongly implicated in malignancy. The work outlines one plausible mechanism by which a genetically abnormal tumor cell could drive the malignant phenotype in healthy tissue through a positive feedback loop of tumor growth and solid stress driven signaling. The work accords with prior studies and reinforces the paradigm that tissue mechanics may be a highly conserved mechanism promoting tumor evolution. What remains unanswered, however, is whether tissue mechanics is solely a tumor promoter or whether it can also initiate cancer. That is, are mechanical cues only relevant under preexisting oncogenic conditions, or can they promote the genetic mutations necessary to cancer initiation? And if so, what molecular mechanisms might be involved to achieve this effect?

The paper highlighted here heralds a new step toward understanding how biophysical cues regulate normal and diseased tissue behavior. Clearly, as additional new technologies emerge that enable researchers to precisely manipulate specific mechanical features of a tissue in vivo, we will at last be able to definitively clarify just how these factors contribute to normal tissue development, homeostasis, and modify disease initiation and progression. As we learn more about how nano, cell-, and tissue-scale material properties and forces are altered in cancer and connect these changes to specific molecular mechanisms, we can only anticipate improvements in the design of diagnostic, prognostic, and therapeutic strategies to counter and prevent mechanically regulated diseases like cancer.

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Abbreviations

ECM	extracellular matrix
FAK	focal adhesion kinase

References

1. Butcher DT, Alliston T, Weaver VM. A tense situation: forcing tumour progression. Nat Rev Cancer. 2009; 9:108–22. [PubMed: 19165226]
2. Stylianopoulos T, Martin JD, Snuderl M, Mpekris F, et al. Coevolution of solid stress and interstitial fluid pressure in tumors during progression: implications for vascular collapse. Cancer Res. 2013; 73:3833–41. [PubMed: 23633490]
3. Lu P, Takai K, Weaver VM, Werb Z. Extracellular matrix degradation and remodeling in development and disease. Cold Spring Harb Perspect Biol. 2011; 3:a005058. [PubMed: 21917992]
4. Boucher Y, Leunig M, Jain RK. Tumor angiogenesis and interstitial hypertension. Cancer Res. 1996; 56:4264–6. [PubMed: 8797602]
5. Greish K. Enhanced permeability and retention (EPR) effect for anticancer nanomedicine drug targeting. Methods Mol Biol. 2010; 624:25–37. [PubMed: 20217587]
6. Heldin C-H, Rubin K, Pietras K, Östman A. High interstitial fluid pressure—an obstacle in cancer therapy. Nat Rev Cancer. 2004; 4:806–13. [PubMed: 15510161]
7. Stylianopoulos T, Martin JD, Snuderl M, Mpekris F, et al. Coevolution of solid stress and interstitial fluid pressure in tumors during progression: implications for vascular collapse. Cancer Res. 2013; 73:3833–41. [PubMed: 23633490]
8. Stylianopoulos T, Martin JD, Chauhan VP, Jain SR, et al. Causes, consequences, and remedies for growth-induced solid stress in murine and human tumors. Proc Natl Acad Sci USA. 2012; 109:15101–8. [PubMed: 22932871]
9. Jain RK, Martin JD, Stylianopoulos T. The role of mechanical forces in tumor growth and therapy. Annu Rev Biomed Eng. 2014; 16:321–46. [PubMed: 25014786]
10. Provenzano PP, Inman DR, Eliceiri KW, Keely PJ. Matrix density-induced mechanoregulation of breast cell phenotype, signaling and gene expression through a FAK-ERK linkage. Oncogene. 2009; 28:4326–43. [PubMed: 19826415]
11. Lu P, Weaver VM, Werb Z. The extracellular matrix: a dynamic niche in cancer progression. J Cell Biol. 2012; 196:395–406. [PubMed: 22351925]
12. Netti PA, Berk DA, Swartz MA, Grodzinsky AJ, et al. Role of extracellular matrix assembly in interstitial transport in solid tumors. Cancer Res. 2000; 60:2497–503. [PubMed: 10811131]
13. Tse JM, Cheng G, Tyrrell JA, Wilcox-Adelman SA, et al. Mechanical compression drives cancer cells toward invasive phenotype. Proc Natl Acad Sci USA. 2012; 109:911–6. [PubMed: 22203958]
14. Pennacchietti S, Michieli P, Galluzzo M, Mazzone M, et al. Hypoxia promotes invasive growth by transcriptional activation of the met protooncogene. Cancer Cell. 2003; 3:347–61. [PubMed: 12726861]
15. Goel S, Duda DG, Xu L, Munn LL, et al. Normalization of the vasculature for treatment of cancer and other diseases. Physiol Rev. 2011; 91:1071–121. [PubMed: 21742796]
16. Pedersen JA, Boschetti F, Swartz MA. Effects of extracellular fiber architecture on cell membrane shear stress in a 3D fibrous matrix. J Biomech. 2007; 40:1484–92. [PubMed: 16987520]

17. Shieh AC, Rozansky HA, Hinz B, Swartz MA. Tumor cell invasion is promoted by interstitial flow-induced matrix priming by stromal fibroblasts. Cancer Res. 2011; 71:790–800. [PubMed: 21245098]
18. Zaman MH, Trapani LM, Sieminski AL, Siemeski A, et al. Migration of tumor cells in 3D matrices is governed by matrix stiffness along with cell-matrix adhesion and proteolysis. Proc Natl Acad Sci USA. 2006; 103:10889–94. [PubMed: 16832052]
19. Haage A, Schneider IC. Cellular contractility and extracellular matrix stiffness regulate matrix metalloproteinase activity in pancreatic cancer cells. FASEB J. 2014; 28:3589–99. [PubMed: 24784579]
20. Pathak A, Kumar S. Independent regulation of tumor cell migration by matrix stiffness and confinement. Proc Natl Acad Sci USA. 2012; 109:10334–9. [PubMed: 22689955]
21. Provenzano PP, Cuevas C, Chang AE, Goel VK, et al. Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma. Cancer Cell. 2012; 21:418–29. [PubMed: 22439937]
22. Olive KP, Jacobetz MA, Davidson CJ, Gopinathan A, et al. Inhibition of Hedgehog signaling enhances delivery of chemotherapy in a mouse model of pancreatic cancer. Science. 2009; 324:1457–61. [PubMed: 19460966]
23. Chauhan VP, Martin JD, Liu H, Lacorre DA, et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumour blood vessels. Nat Commun. 2013; 4:2516. [PubMed: 24084631]
24. Levental KR, Yu H, Kass L, Lakins JN, et al. Matrix crosslinking forces tumor progression by enhancing integrin signaling. Cell. 2009; 139:891–906. [PubMed: 19931152]
25. Samuel MS, Lopez JI, McGhee EJ, Croft DR, et al. Actomyosin-mediated cellular tension drives increased tissue stiffness and β-catenin activation to induce epidermal hyperplasia and tumor growth. Cancer Cell. 2011; 19:776–91. [PubMed: 21665151]
26. Polacheck WJ, Zervantonakis IK, Kamm RD. Tumor cell migration in complex microenvironments. Cell Mol Life Sci. 2012; 70:1335–56. [PubMed: 22926411]
27. Fernández-Sánchez ME, Barbier S, Whitehead J, Béalle G, et al. Mechanical induction of the tumorigenic β-catenin pathway by tumour growth pressure. Nature. 2015; 523:92–5. [PubMed: 25970250]
28. Paszek MJ, Zahir N, Johnson KR, Lakins JN, et al. Tensional homeostasis and the malignant phenotype. Cancer Cell. 2005; 8:241–54. [PubMed: 16169468]
29. Friedland JC, Lee MH, Boettiger D. Mechanically activated integrin switch controls alpha5beta1 function. Science. 2009; 323:642–4. [PubMed: 19179533]
30. Mitra SK, Schlaepfer DD. Integrin-regulated FAK-Src signaling in normal and cancer cells. Curr Opin Cell Biol. 2006; 18:516–23. [PubMed: 16919435]
31. Kim J-H, Asthagiri AR. Matrix stiffening sensitizes epithelial cells to EGF and enables the loss of contact inhibition of proliferation. J Cell Sci. 2011; 124:1280–7. [PubMed: 21429934]
32. Mouw JK, Yui Y, Damiano L, Bainer RO, et al. Tissue mechanics modulate microRNA-dependent PTEN expression to regulate malignant progression. Nat Med. 2014; 20:360–7. [PubMed: 24633304]
33. Pickup MW, Laklai H, Acerbi I, Owens P, et al. Stromally derived lysyl oxidase promotes metastasis of transforming growth factor-β-deficient mouse mammary carcinomas. Cancer Res. 2013; 73:5336–46. [PubMed: 23856251]
34. Li L, Hanahan D. Hijacking the neuronal NMDAR signaling circuit to promote tumor growth and invasion. Cell. 2013; 153:86–100. [PubMed: 23540692]
35. MacDonald BT, Tamai K, He X. Wnt/beta-catenin signaling: components, mechanisms, and diseases. Dev Cell. 2009; 17:9–26. [PubMed: 19619488]
36. Kimelman D, Xu W. Beta-catenin destruction complex: insights and questions from a structural perspective. Oncogene. 2006; 25:7482–91. [PubMed: 17143292]
37. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu Rev Cell Dev Biol. 2004; 20:781–810. [PubMed: 15473860]

38. Brunet T, Bouclet A, Ahmadi P, Mitrossilis D, et al. Evolutionary conservation of early mesoderm specification by mechanotransduction in Bilateria. Nat Commun. 2013; 4:2821. [PubMed: 24281726]

39. Burgers TA, Williams BO. Regulation of Wnt/β-catenin signaling within and from osteocytes. Bone. 2013; 54:244–9. [PubMed: 23470835]

40. Ehnes DD, Price FD, Shrive NG, Hart DA, et al. Embryonic stem cell-derived osteocytes are capable of responding to mechanical oscillatory hydrostatic pressure. J Biomech. 2015; 48:1915–21. [PubMed: 25936968]

41. Desprat N, Supatto W, Pouille P-A, Beaurepaire E, et al. Tissue deformation modulates twist expression to determine anterior midgut differentiation in Drosophila embryos. Dev Cell. 2008; 15:470–7. [PubMed: 18804441]

42. Ladoux B, Nelson WJ, Yan J, Mège RM. The mechanotransduction machinery at work at adherens junctions. Integr Biol (Camb). 2015 in press. doi: 10.1039/C5IB00070J.

43. Dow LE, O'Rourke KP, Simon J, Tschaharganeh DF, et al. Apc restoration promotes cellular differentiation and reestablishes crypt homeostasis in colorectal cancer. Cell. 2015; 161:1539–52. [PubMed: 26091037]

44. Whitehead J, Vignjevic D, Fütterer C, Beaurepaire E, et al. Mechanical factors activate beta-catenin-dependent oncogene expression in APC mouse colon. HFSP J. 2008; 2:286–94. [PubMed: 19404440]

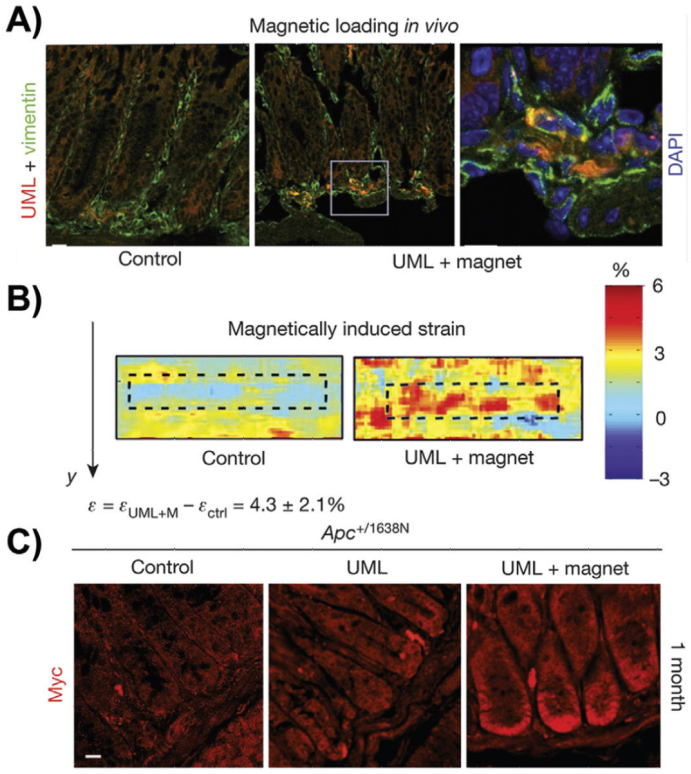

Figure 1.

A: Rhodamine-labeled ultramagnetic liposomes (UML) were placed in vivo and can be seen to colocalize with vimentin. **B**: Strain map of control and magnet + UML-injected colon in mice. **C**: Increased expression of β-catenin target, MYC, as a result of applied pressure after a month. From Fernández-Sánchez et al. [27].

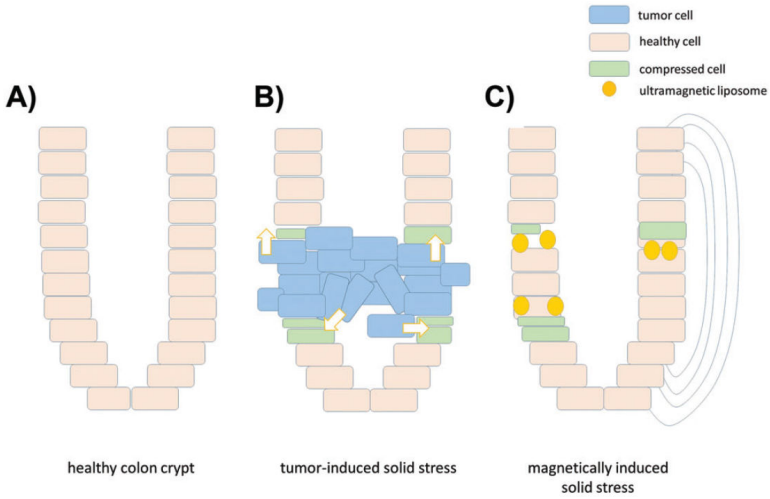

Figure 2.

Summary of experiments performed in the highlighted article. In contrast to normal colon (**A**), solid stress from the large tumor mass in cancer exerts pressure on neighboring, normal cells and induces development of a malignant phenotype in these cells (**B**). Fernández-Sánchez et al. replicated this effect in healthy colon crypts (**C**) using ultramagnetic liposomes and an implanted magnet, which exerted pressure on normal cells and activated β-catenin signaling to drive adoption of tumor cell-like behavior.