(Rückle et al., 2006), and the development of PI3Kγ-selective compounds has been slower than other target profiles. Although the conclusions of Schmid et al. (2011) need to be validated in other models, the current data support the novel conclusion that the antiinflammatory potential of PI3Kγ inhibitors might be harnessed to disrupt the tumor microenvironment and slow the progression of cancer. The fact that most solid tumor cells do not express PI3Kγ should limit the development of resistance to PI3Kγ inhibitors. These considerations should increase momentum for PI3Kγ inhibitor programs. To be sure, there remain challenges to developing treatments targeting cancer inflammation. Should such agents be given as preventive therapy, or will they be effective in treating established malignancies? These questions can be addressed initially through additional preclinical studies. If PI3Kγ-targeted agents can limit the growth of established tumors, an important implication is that drugs targeting all class I PI3Ks (or just PI3Kα and PI3Kγ) should be more effective than selective PI3Kα inhibitors, even in patients whose tumors are driven by *PI3KCA* mutations.

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ROCK-Driven Actomyosin Contractility Induces Tissue Stiffness and Tumor Growth

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The tumor environment consists of tumor-associated cells, such as macrophages, fibroblasts, and extracellular matrix, and has an important impact on tumor progression. In this issue of *Cancer Cell,* Samuel et al. show that ROCK-driven actomyosin contractility increases tissue stiffness affecting epidermal homeostasis, as well as tumor growth and progression.

Tissues consist of cells and extracellular matrix (ECM), and cells are tightly linked to their extracellular environment through adhesion receptors such as integrins. Within a tissue, remodeling of the ECM can occur as part of normal physiological processes or in disease. ECM remodeling involves both the physical force of tension acting on the ECM and enzymatic action; for example, by extracellular proteases or enzymes that crosslink ECM components such as collagen. An imbalance in the relationship between cells and the extracellular environment is found in diseases such as cancer, and there is strong evidence that increased tissue stiffness contributes to tumor progression (Levental et al., 2009; Paszek et al., 2005). Indeed, increased tissue stiffness is the basis of physical examination by palpation for cancer. Tissue stiffening may result from ECM remodeling that drives integrin clustering at the cell surface and subsequent cytoskeletal changes, resulting in changes of intracellular tension. Intracellular tension arises through the action of myosin II in generating actomyosin contractility. Actomyosin contractility has multiple other roles in addition to muscle contraction. It is essential for cyokinesis in mitosis, cell adhesion, cell shape, and cell movement (Vicente-Manzanares et al., 2011). The level of actomyosin contractility in tumor cells is a key determinant of different modes of cell movement (Sanz-Moreno and Marshall, 2010). An important regulator of actomyosin contractility is the family of Rho-associated coiled-coil forming protein serine/threonine kinases (ROCKI and ROCKII) that are activated by Rho GTPases RhoA and RhoC. ROCKI and II generate contractile force through phosphorylation of the myosin-binding subunit of myosin phosphatase (MYPT1), LIM kinase 2 (LIMK2), and possibly myosin regulatory light chain (MLC2) (Figure 1A).

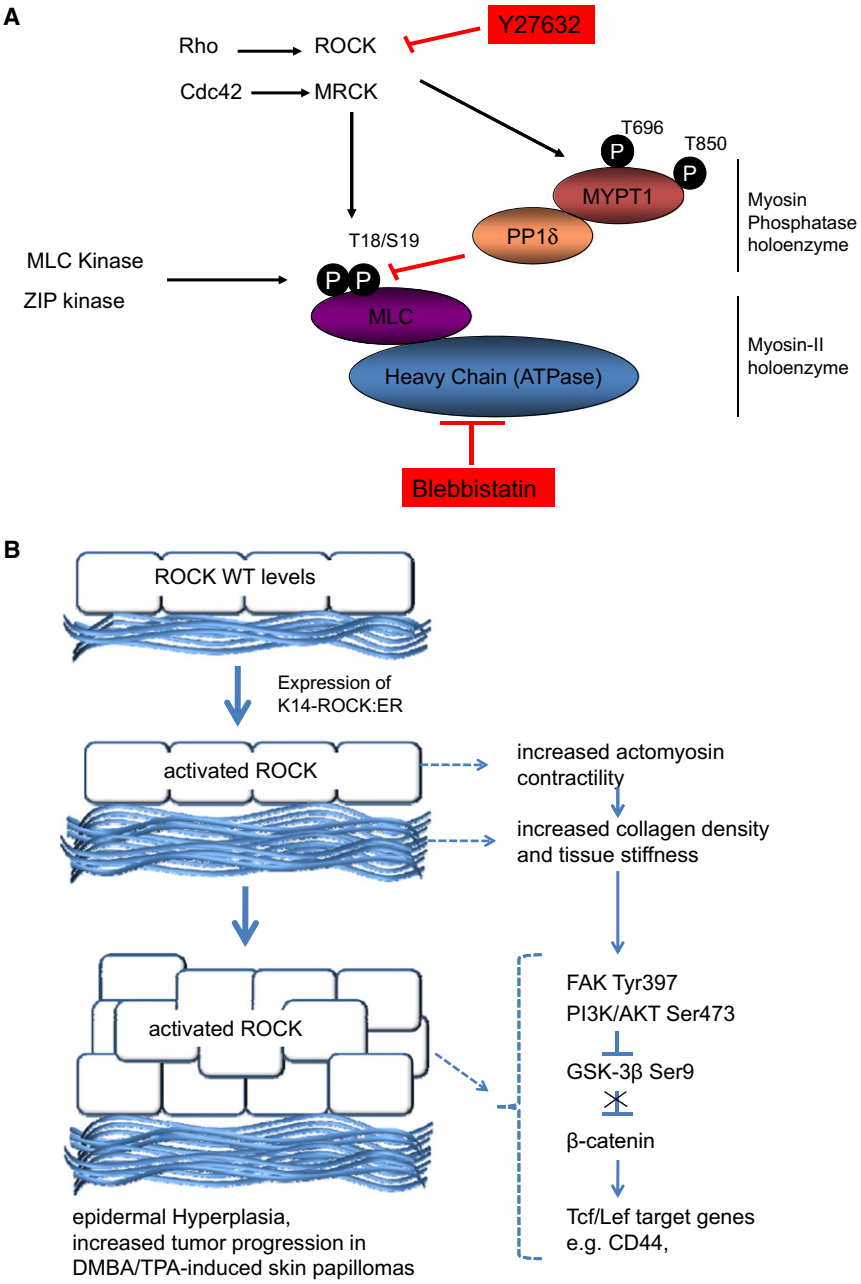

Figure 1. Signaling Pathways to Actomyosin Contractility and Effects of Increased Intracellular Tension on Skin Homeostasis and Tumor Growth

(A) Regulation of actomyosin contractility by Rho family GTPases. Phosphorylation of MLC2, the regulatory subunit of myosin, activates the holoenzyme and generates actomyosin contractility. Rho family GTPases regulate myosin phosphatase, Rho kinase (ROCK), or myotonic dystrophy kinase-related Cdc42 binding kinase (MRCK), which phosphorylate the myosin-binding subunit of myosin phosphatase (MYPT1), inactivating myosin phosphatase to prevent dephosphorylation of MLC2. Actomyosin contractility can be blocked by blebbistatin, which directly inhibits Myosin II ATPase activity or treatment with ROCK inhibitors such as Y27632, which lead to increased myosin phosphatase activity.

(B) K14-driven expression of ROCK:ER in mouse skin induces actomyosin contractility, resulting in increased collagen deposition and tissue stiffness. Intracellular signaling is promoted by the engagement of integrins and activation of focal adhesion kinase (FAK) leading to β-catenin-induced gene expression. Expression of ROCK:ER in DMBA/TPA-treated mice induces a significant increase in tumor burden compared with controls.

The skin is constantly exposed to environmental stresses, and therefore a constant remodeling process is required to maintain barrier integrity and protection from external forces. Thus, it provides a good system to study the effects of intracellular tension. Samuel et al. (2009) previously generated a mouse model that expresses a chimeric protein, ROCK:ER, consisting of the kinase domain of human ROCK II fused to a tamoxifen-regulated mutant estrogen receptor (ER) and enhanced green fluorescent protein (EGFP) under the control of the K14 promoter. Samuel et al. (2011) now use this model to study ROCK-induced actomyosin contractility in tissue homeostasis and tumor progression. Upon induction of ROCK activity, Samuel et al. (2011) observed an increase in collagen density and tissue stiffness, as well as epidermal hyperproliferation compared with wild-type skin or skin expressing a kinase dead (KD) version of the ROCK:ER protein. Interestingly, this shows that ROCK:ER-induced intracellular contractility affected two seemingly different processes: ECM remodeling and increased tissue stiffness on one hand and cellular proliferation on the other. The increased proliferation appears to be a consequence of enhanced β−catenin signaling. β-Catenin is known to be a regulator of epidermal proliferation and is responsive to mechanical tension. Samuel et al. (2011) showed that, following induction of ROCK activity in skin, β-catenin localization changed from membranous to cytoplasmic and nuclear, and overall β-catenin levels increased significantly. In contrast, E-cadherin, with which β-catenin interacts at cell-cell junctions, remained at the cell membrane. Importantly, nuclear β-catenin was found to be in the activated form, and this was associated with an increase in glycogen synthase kinase-3 (GSK-3β) phosphorylation. To confirm the role of β-catenin in ROCK-induced hyperproliferation, β-catenin expression was ablated in the skin, which resulted in reduced proliferation and expression of the target genes, CD44 and CyclinD1.

To show that the consequences of increased ROCK activity were a result of increased actomyosin contractility, the authors tested whether inhibiting mediators of contractility downstream of ROCK would block the induced epidermal hyperproliferation. Indeed, application of an inhibitor of myosin II ATPase activity

(blebbistatin) or an inhibitor of LIMK, a kinase that acts downstream of ROCK to promote actin assembly, blocked skin thickening and reduced β-catenin levels in K14-ROCK:ER mice. Similarly, the increase in collagen deposition was found to be reduced.

To test whether ROCK activation would impact tumor growth and progression, skin papillomas were induced by two-step chemical tumorigenesis using dimethylbenz[a]anthracene (DMBA) and 12-O-tetradecanoylphorbol-13-acetate (TPA). Through a mechanism involving mutation of HRAS and subsequent MAP-kinase activation, skin papillomas appear and a small proportion progress to invasive carcinomas. When the inducible ROCK:ER mice were used in the two-stage chemical carcinogenesis protocol, induction of ROCK activity increased total papilloma burden and accelerated progression to carcinomas compared with controls. Moreover, total and nuclear β-catenin levels were significantly increased in papillomas in the ROCK:ER mice, indicating that the pathways regulating skin thickening are also important during tumor progression. Interestingly, the authors showed that simultaneous treatment of mouse skin with DMBA/TPA and the ROCK inhibitor Y-27632 resulted in a significantly lower papilloma burden and a lower conversion rate. It will be of great interest to determine the effects of blocking ROCK activity on established papillomas and carcinomas. Importantly, Samuel et al. (2011) provide evidence that ROCK signaling is frequently upregulated in human skin carcinomas. Further work will be required to provide a detailed picture of the levels of ROCK and ROCK signaling to tumor grade and to extend these studies to other tumor types.

Without doubt, Samuel et al. (2011) have provided strong evidence for ROCK-mediated intracellular contractility driving tumorigenesis by affecting ECM deposition, remodeling, and tissue stiffness. Importantly, they show that increased tissue stiffness results from increased collagen deposition and crosslinking following increased actomyosin contractility (Figure 1B). Why there is an increased collagen deposition remains unclear, whereas the mechanism for an increase in levels of β-catenin and its transcriptional activity may depend on increased integrin signaling (Figure 1B). In the experimental system used in this study, elevated actomyosin contractility is generated in the tumor cells themselves; however, other work suggests that tumor-associated cells such as carcinoma-associated fibroblasts can generate actomyosin contractility for extracellular matrix remodeling (Gaggioli et al., 2007). Furthermore, there is evidence that some cancers may harbor mutations that reduce actomyosin contractility (Brognard et al., 2011). Thus, the study of the roles of actomyosin contractility is likely to generate many new insights into tumor biology.

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Turning Reciprocal Feedback Regulation into Combination Therapy

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Two recent *Cancer Cell* articles report the discovery of reciprocal feedback regulation between androgenic and *PTEN* loss/PI3K-AKT signaling in prostate cancer. Both studies link endocrine regulation with a common oncogenic pathway, which led to the development of a combination therapeutic approach with immediate application in prostate cancer.

The exquisite sensitivity of the prostate gland to androgenic steroids has provided a foothold for the development of systemic prostate cancer therapy for more than seventy years (Huggins and Hodges, 1941). A sustained strategic approach that focused on inhibiting this unique signaling pathway led to the use of androgen-deprivation and antiandrogenic therapies for