

Michael P. Sheetz



Columbia University
Biological Sciences
New York, N.Y. 10027

E-mail ms2001@columbia.edu
[Return to Biology HomePage](#)

Research Highlights

Matrix Forces on the Cytoskeleton Act as Critical Signals

Cancer and uncontrolled cell growth involve the improper processing of environmental cues and one of the most important cues is force on the extracellular matrix (ECM) that supports the cell. Normal cells generate force on external matrices as a requirement for growth whereas transformed cells can grow on soft agar, which will not support force. Using laser tweezers microscopy to apply defined forces to matrix-coated beads and mutant cell lines, we are studying the molecular pathways of force sensation and force generation (Galbraith and Sheetz, 1999). Our working hypothesis is that force on cytoskeleton-integrin-ECM linkages signals to a tyrosine phosphatase that starts a cascade of enzyme reactions that causes reinforcement of the linkage as well as signaling to the cell (Choquet et al., 1997). Tyrosine kinases such as c-Src reverse reinforcement (Felsenfeld et al., 1999) and enable the cell to attach and detach for migration and matrix remodeling. Current studies are focussing on 1) the cytoskeleton component that senses force, 2) the phosphatase that causes reinforcement, 3) the integrin-cytoskeleton linkage, 4) coordination of motility and force on matrix fibers, and 5) the molecular basis of reinforcement.

Membrane (Lipid)-Cytoskeleton Adhesion Controls Cell Functions

We have proposed that the rates of mechanochemical processes, such as endocytosis, membrane extension and membrane resealing after cell wounding, might be controlled not only biochemically - through interaction with regulatory proteins - but also physically, through an apparently continuous adhesion between the plasma membrane lipids and the cytoskeleton proteins (Sheetz, 2001). Numerous studies of membrane-cytoskeleton adhesion using laser tweezers to form tethers on the plasma membrane have shown that the tether force is inversely proportional to the rates of endocytosis (Dai et al., 1997; Raucher and Sheetz, 1999), membrane extension (Raucher and Sheetz, 1999), and membrane resealing. In studies of the molecular basis of the adhesion, the level of phosphatidylinositol 4,5 diphosphate (PIP₂) correlates directly with adhesion and the tether force (Raucher et al., 2000). Now we are exploring how the free level of PIP₂ is regulated and which cytoskeleton proteins interact with PIP₂. Lipid control of membrane-cytoskeleton adhesion has important implications for membrane structure and the control of a wide variety of cell functions.

Organelle Traffic in Neurons and Polarized Cells

We have a long-standing interest in the molecular basis of organelle transport in neurons. Recent studies are focussed on the control of mitochondrial movements since they are critical organelles that move in two directions on microtubules and interact with myosin. Thus, they are ideal for studying control of motor switching and regulation of motility. Using in vivo and in vitro assays of directional movement of mitochondria on microtubules, we have found a critical role for inositol lipids in the cytoplasmic dynein but not kinesin-dependent movements. Further, we have found a high level of myosin V binding to mitochondria in the periphery of neurons (Miller and Sheetz, 2000). Now we will analyze the basis of control whether through vesicle binding or motor activation. Additional projects are focussed on membrane binding sites for kinesin such as kinectin and the role of tension in ER and Golgi networks.

Bacterial Pilus Retraction

The retraction of bacterial pili appears to constitute a novel motility mechanism (Merz et al.,

2000), which involves dissociation of pilus subunits into the inner membrane. We are now testing this model to understand the molecular basis of force generation.

Current Projects:

Julia Sable (Lab Manager/ Director of Confocal Microscopy) Membrane-cytoskeleton adhesion and PIP2 levels

[Return to Biology Homepage](#)

Recent Publications from the Sheetz Lab:

- 1: Zhang X, Jiang G, Cai Y, Monkley SJ, Critchley DR, Sheetz MP.
Talin depletion reveals independence of initial cell spreading from integrin activation and traction.
Nat Cell Biol. 2008 Aug 17. [Epub ahead of print]
PMID: 18711359 [PubMed - as supplied by publisher]
- 2: Perez TD, Tamada M, Sheetz MP, Nelson WJ.
Immediate-early signaling induced by E-cadherin engagement and adhesion.
J Biol Chem. 2008 Feb 22;283(8):5014-22. Epub 2007 Dec 17.
PMID: 18089563 [PubMed - indexed for MEDLINE]
- 3: von Wichert G, Krndija D, Schmid H, von Wichert G, Haerter G, Adler G, Seufferlein T, Sheetz MP.
Focal adhesion kinase mediates defects in the force-dependent reinforcement of initial integrin-cytoskeleton linkages in metastatic colon cancer cell lines.
Eur J Cell Biol. 2008 Jan;87(1):1-16. Epub 2007 Sep 27.
PMID: 17904248 [PubMed - indexed for MEDLINE]
- 4: Kostic A, Sap J, Sheetz MP.
RPTPalpha is required for rigidity-dependent inhibition of extension and differentiation of hippocampal neurons.
J Cell Sci. 2007 Nov 1;120(Pt 21):3895-904. Epub 2007 Oct 16.
PMID: 17940065 [PubMed - indexed for MEDLINE]
- 5: Ahmed I, Ponery AS, Nur-E-Kamal A, Kamal J, Meshel AS, Sheetz MP, Schindler M, Meiners S.
Morphology, cytoskeletal organization, and myosin dynamics of mouse embryonic fibroblasts cultured on nanofibrillar surfaces.
Mol Cell Biochem. 2007 Jul;301(1-2):241-9. Epub 2007 Feb 9.
PMID: 17294137 [PubMed - indexed for MEDLINE]
- 6: Sims TN, Soos TJ, Xenias HS, Dubin-Thaler B, Hofman JM, Waite JC, Cameron TO, Thomas VK, Varma R, Wiggins CH, Sheetz MP, Littman DR, Dustin ML.
Opposing effects of PKCtheta and WASp on symmetry breaking and relocation of the immunological synapse.
Cell. 2007 May 18;129(4):773-85.
PMID: 17512410 [PubMed - indexed for MEDLINE]
- 7: Calloway NT, Choob M, Sanz A, Sheetz MP, Miller LW, Cornish VW.
Optimized fluorescent trimethoprim derivatives for in vivo protein labeling.
Chembiochem. 2007 May 7;8(7):767-74.
PMID: 17378009 [PubMed - indexed for MEDLINE]
- 8: Giannone G, Dubin-Thaler BJ, Rossier O, Cai Y, Chaga O, Jiang G, Beaver W,

D √ obereiner HG, Freund Y, Borisy G, Sheetz MP.
Lamellipodial actin mechanically links myosin activity with adhesion-site formation.

Cell. 2007 Feb 9;128(3):561-75.

PMID: 17289574 [PubMed - indexed for MEDLINE]

9: Tamada M, Perez TD, Nelson WJ, Sheetz MP.

Two distinct modes of myosin assembly and dynamics during epithelial wound closure.

J Cell Biol. 2007 Jan 1;176(1):27-33. Erratum in: J Cell Biol. 2007 Feb 12;176(4):545.

PMID: 17200415 [PubMed - indexed for MEDLINE]

10: De Vos KJ, Sheetz MP.

Visualization and quantification of mitochondrial dynamics in living animal cells.

Methods Cell Biol. 2007;80:627-82. Review. No abstract available.

PMID: 17445716 [PubMed - indexed for MEDLINE]

11: Sawada Y, Tamada M, Dubin-Thaler BJ, Cherniavskaya O, Sakai R, Tanaka S, Sheetz MP.

Force sensing by mechanical extension of the Src family kinase substrate p130Cas. Cell. 2006 Dec 1;127(5):1015-26.

PMID: 17129785 [PubMed - indexed for MEDLINE]

12: Cai Y, Biais N, Giannone G, Tanase M, Jiang G, Hofman JM, Wiggins CH, Silberzan P, Buguin A, Ladoux B, Sheetz MP.

Nonmuscle myosin IIA-dependent force inhibits cell spreading and drives F-actin flow.

Biophys J. 2006 Nov 15;91(10):3907-20. Epub 2006 Aug 18.

PMID: 16920834 [PubMed - indexed for MEDLINE]

13: D √ obereiner HG, Dubin-Thaler BJ, Hofman JM, Xenias HS, Sims TN, Giannone G, Dustin ML, Wiggins CH, Sheetz MP.

Lateral membrane waves constitute a universal dynamic pattern of motile cells.

Phys Rev Lett. 2006 Jul 21;97(3):038102. Epub 2006 Jul 20.

PMID: 16907546 [PubMed - indexed for MEDLINE]

14: Kostic A, Sheetz MP.

Fibronectin rigidity response through Fyn and p130Cas recruitment to the leading edge.

Mol Biol Cell. 2006 Jun;17(6):2684-95. Epub 2006 Apr 5.

PMID: 16597701 [PubMed - indexed for MEDLINE]

15: Miller KE, Sheetz MP.

Direct evidence for coherent low velocity axonal transport of mitochondria.

J Cell Biol. 2006 May 8;173(3):373-81.

PMID: 16682527 [PubMed - indexed for MEDLINE]

16: Giannone G, Sheetz MP.

Substrate rigidity and force define form through tyrosine phosphatase and kinase pathways.

Trends Cell Biol. 2006 Apr;16(4):213-23. Epub 2006 Mar 10. Review.

PMID: 16529933 [PubMed - indexed for MEDLINE]

17: Jiang G, Huang AH, Cai Y, Tanase M, Sheetz MP.

Rigidity sensing at the leading edge through α v β 3 integrins and RPTP α .

Biophys J. 2006 Mar 1;90(5):1804-9. Epub 2005 Dec 9.
PMID: 16339875 [PubMed - indexed for MEDLINE]

18: Sheetz MP, Sable JE, D \check{a} bereiner HG.
Continuous membrane-cytoskeleton adhesion requires continuous accommodation to lipid and cytoskeleton dynamics.
Annu Rev Biophys Biomol Struct. 2006;35:417-34. Review.
PMID: 16689643 [PubMed - indexed for MEDLINE]

19: von Wichert G, Sheetz MP.
Mechanisms of disease: the biophysical interpretation of the ECM affects physiological and pathophysiological cellular behavior.
Z Gastroenterol. 2005 Dec;43(12):1329-36. Review.
PMID: 16315129 [PubMed - indexed for MEDLINE]

20: De Vos KJ, Allan VJ, Grierson AJ, Sheetz MP.
Mitochondrial function and actin regulate dynamin-related protein 1-dependent mitochondrial fission.
Curr Biol. 2005 Apr 12;15(7):678-83.
PMID: 15823542 [PubMed - indexed for MEDLINE]

21: D \check{a} bereiner HG, Dubin-Thaler BJ, Giannone G, Sheetz MP.
Force sensing and generation in cell phases: analyses of complex functions.
J Appl Physiol. 2005 Apr;98(4):1542-6. Review.
PMID: 15772064 [PubMed - indexed for MEDLINE]

22: Miller LW, Cai Y, Sheetz MP, Cornish VW.
In vivo protein labeling with trimethoprim conjugates: a flexible chemical tag.
Nat Methods. 2005 Apr;2(4):255-7.
PMID: 15782216 [PubMed - indexed for MEDLINE]

23: Meshel AS, Wei Q, Adelstein RS, Sheetz MP.
Basic mechanism of three-dimensional collagen fibre transport by fibroblasts.
Nat Cell Biol. 2005 Feb;7(2):157-64. Epub 2005 Jan 16.
PMID: 15654332 [PubMed - indexed for MEDLINE]

24: Tamada M, Sheetz MP, Sawada Y.
Activation of a signaling cascade by cytoskeleton stretch.
Dev Cell. 2004 Nov;7(5):709-18.
PMID: 15525532 [PubMed - indexed for MEDLINE]

25: D \check{a} bereiner HG, Dubin-Thaler B, Giannone G, Xenias HS, Sheetz MP.
Dynamic phase transitions in cell spreading.
Phys Rev Lett. 2004 Sep 3;93(10):108105. Epub 2004 Sep 2.
PMID: 15447457 [PubMed - indexed for MEDLINE]

26: Maier B, Koomey M, Sheetz MP.
A force-dependent switch reverses type IV pilus retraction.
Proc Natl Acad Sci U S A. 2004 Jul 27;101(30):10961-6. Epub 2004 Jul 15.
PMID: 15256598 [PubMed - indexed for MEDLINE]

27: Maier B, Chen I, Dubnau D, Sheetz MP.
DNA transport into *Bacillus subtilis* requires proton motive force to generate large molecular forces.
Nat Struct Mol Biol. 2004 Jul;11(7):643-9. Epub 2004 Jun 6.
PMID: 15184891 [PubMed - indexed for MEDLINE]

28: Miller KE, Sheetz MP.

Axonal mitochondrial transport and potential are correlated.

J Cell Sci. 2004 Jun 1;117(Pt 13):2791-804. Epub 2004 May 18.

PMID: 15150321 [PubMed - indexed for MEDLINE]

29: Upadhyaya A, Sheetz MP.

Tension in tubulovesicular networks of Golgi and endoplasmic reticulum membranes.

Biophys J. 2004 May;86(5):2923-8.

PMID: 15111408 [PubMed - indexed for MEDLINE]

30: Miller LW, Sable J, Goelet P, Sheetz MP, Cornish VW.

Methotrexate conjugates: a molecular in vivo protein tag.

Angew Chem Int Ed Engl. 2004 Mar 19;43(13):1672-5. No abstract available.

PMID: 15038033 [PubMed - indexed for MEDLINE]

31: Dubin-Thaler BJ, Giannone G, Döbereiner HG, Sheetz MP.

Nanometer analysis of cell spreading on matrix-coated surfaces reveals two distinct cell states and STEPs.

Biophys J. 2004 Mar;86(3):1794-806.

PMID: 14990505 [PubMed - indexed for MEDLINE]

32: Giannone G, Dubin-Thaler BJ, Döbereiner HG, Kieffer N, Bresnick AR, Sheetz MP.

Periodic lamellipodial contractions correlate with rearward actin waves.

Cell. 2004 Feb 6;116(3):431-43.

PMID: 15016377 [PubMed - indexed for MEDLINE]

33: Kwik J, Boyle S, Fooksman D, Margolis L, Sheetz MP, Edidin M.

Membrane cholesterol, lateral mobility, and the phosphatidylinositol

4,5-bisphosphate-dependent organization of cell actin.

Proc Natl Acad Sci U S A. 2003 Nov 25;100(24):13964-9. Epub 2003 Nov 11.

PMID: 14612561 [PubMed - indexed for MEDLINE]

34: Giannone G, Jiang G, Sutton DH, Critchley DR, Sheetz MP.

Talin1 is critical for force-dependent reinforcement of initial

integrin-cytoskeleton bonds but not tyrosine kinase activation.

J Cell Biol. 2003 Oct 27;163(2):409-19.

PMID: 14581461 [PubMed - indexed for MEDLINE]

35: von Wichert G, Haimovich B, Feng GS, Sheetz MP.

Force-dependent integrin-cytoskeleton linkage formation requires downregulation of focal complex dynamics by Shp2.

EMBO J. 2003 Oct 1;22(19):5023-35.

PMID: 14517241 [PubMed - indexed for MEDLINE]

36: De Vos KJ, Sable J, Miller KE, Sheetz MP.

Expression of phosphatidylinositol (4,5) bisphosphate-specific pleckstrin homology domains alters direction but not the level of axonal transport of mitochondria.

Mol Biol Cell. 2003 Sep;14(9):3636-49. Epub 2003 Jul 11.

PMID: 12972553 [PubMed - indexed for MEDLINE]

37: Jiang G, Giannone G, Critchley DR, Fukumoto E, Sheetz MP.

Two-piconewton slip bond between fibronectin and the cytoskeleton depends on talin.

Nature. 2003 Jul 17;424(6946):334-7.

PMID: 12867986 [PubMed - indexed for MEDLINE]

38: von Wichert G, Jiang G, Kostic A, De Vos K, Sap J, Sheetz MP.

RPTP-alpha acts as a transducer of mechanical force on
alphav/beta3-integrin-cytoskeleton linkages.

J Cell Biol. 2003 Apr 14;161(1):143-53. Epub 2003 Apr 7.

PMID: 12682088 [PubMed - indexed for MEDLINE]

39: Maier B, Potter L, So M, Long CD, Seifert HS, Sheetz MP.

Single pilus motor forces exceed 100 pN.

Proc Natl Acad Sci U S A. 2002 Dec 10;99(25):16012-7. Epub 2002 Nov 22. Erratum
in: Proc Natl Acad Sci U S A. 2003 May 13;100(10):6287.

PMID: 12446837 [PubMed - indexed for MEDLINE]

40: Galbraith CG, Yamada KM, Sheetz MP.

The relationship between force and focal complex development.

J Cell Biol. 2002 Nov 25;159(4):695-705.

PMID: 12446745 [PubMed - indexed for MEDLINE]

41: Niebuhr K, Giuriato S, Pedron T, Philpott DJ, Gaits F, Sable J, Sheetz MP,
Parsot C, Sansonetti PJ, Payraastre B.

Conversion of PtdIns(4,5)P(2) into PtdIns(5)P by the *S. flexneri* effector IpgD
reorganizes host cell morphology.

EMBO J. 2002 Oct 1;21(19):5069-78.

PMID: 12356723 [PubMed - indexed for MEDLINE]

42: Coussen F, Choquet D, Sheetz MP, Erickson HP.

Trimers of the fibronectin cell adhesion domain localize to actin filament
bundles and undergo rearward translocation.

J Cell Sci. 2002 Jun 15;115(Pt 12):2581-90.

PMID: 12045228 [PubMed - indexed for MEDLINE]

43: Sawada Y, Sheetz MP.

Force transduction by Triton cytoskeletons.

J Cell Biol. 2002 Feb 18;156(4):609-15. Epub 2002 Feb 11.

PMID: 11839769 [PubMed - indexed for MEDLINE]

44: Suzuki K, Sheetz MP.

Binding of cross-linked glycosylphosphatidylinositol-anchored proteins to
discrete actin-associated sites and cholesterol-dependent domains.

Biophys J. 2001 Oct;81(4):2181-9.

PMID: 11566789 [PubMed - indexed for MEDLINE]

45: Raucher D, Sheetz MP.

Phospholipase C activation by anesthetics decreases membrane-cytoskeleton
adhesion.

J Cell Sci. 2001 Oct;114(Pt 20):3759-66.

PMID: 11707527 [PubMed - indexed for MEDLINE]

46: Galbraith CG, Sheetz MP.

Cell traction.

Curr Protoc Cell Biol. 2001 May;Chapter 12:Unit 12.3. Review.

PMID: 18228317 [PubMed - indexed for MEDLINE]

47: Sheetz MP.

Cell control by membrane-cytoskeleton adhesion.

Nat Rev Mol Cell Biol. 2001 May;2(5):392-6. Review.

PMID: 11331914 [PubMed - indexed for MEDLINE]

48: Merz AJ, So M, Sheetz MP.
Pilus retraction powers bacterial twitching motility.
Nature. 2000 Sep 7;407(6800):98-102.
PMID: 10993081 [PubMed - indexed for MEDLINE]

49: Suzuki K, Sterba RE, Sheetz MP.
Outer membrane monolayer domains from two-dimensional surface scanning resistance
measurements.
Biophys J. 2000 Jul;79(1):448-59.
PMID: 10866970 [PubMed - indexed for MEDLINE]

50: Wang Z, Sheetz MP.
The C-terminus of tubulin increases cytoplasmic dynein and kinesin processivity.
Biophys J. 2000 Apr;78(4):1955-64.
PMID: 10733974 [PubMed - indexed for MEDLINE]