

# Effect of TGF beta-1 on Epithelial Mesenchymal Transformation

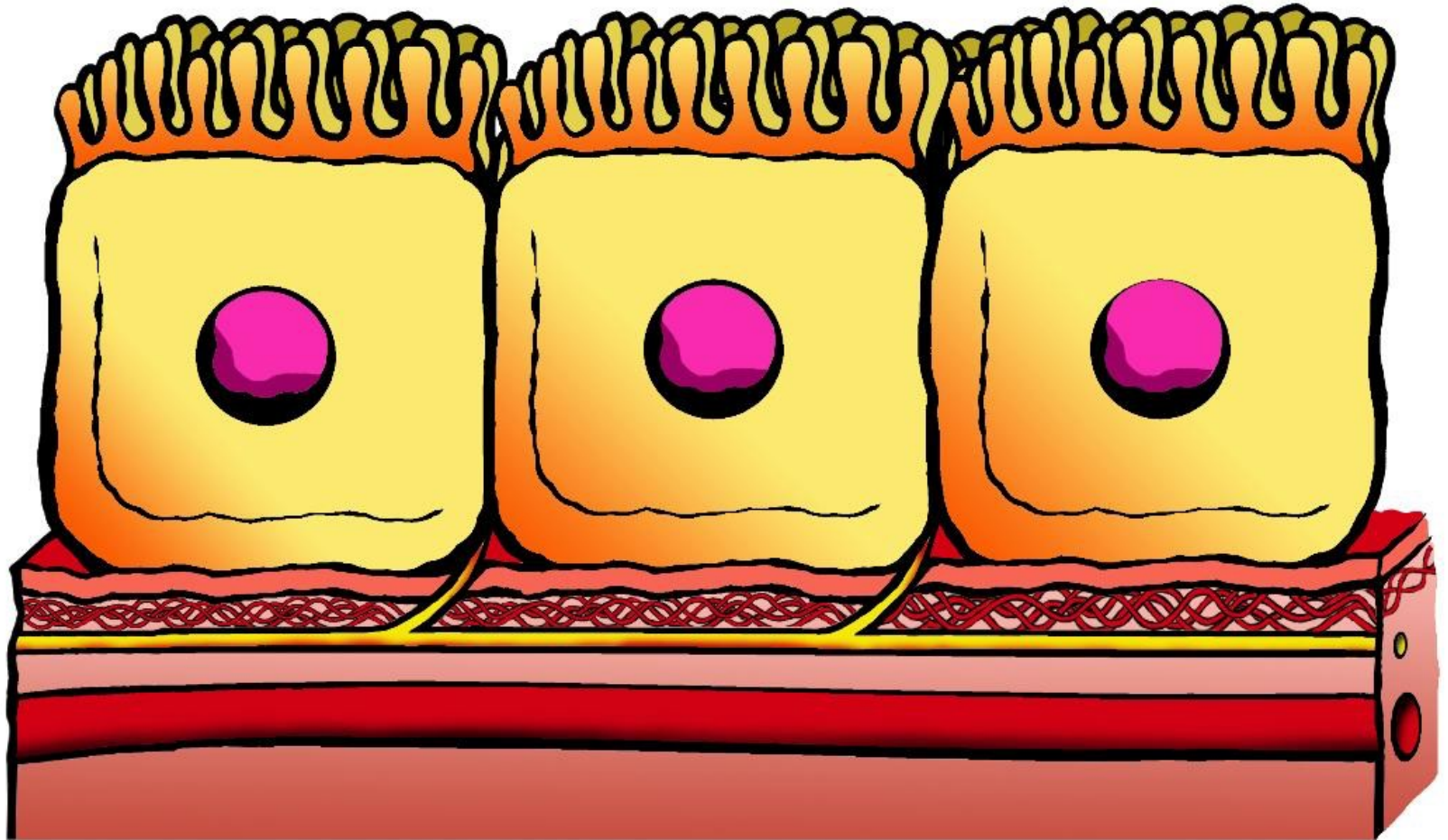


**Dr. Michael E. Rothman, MD**

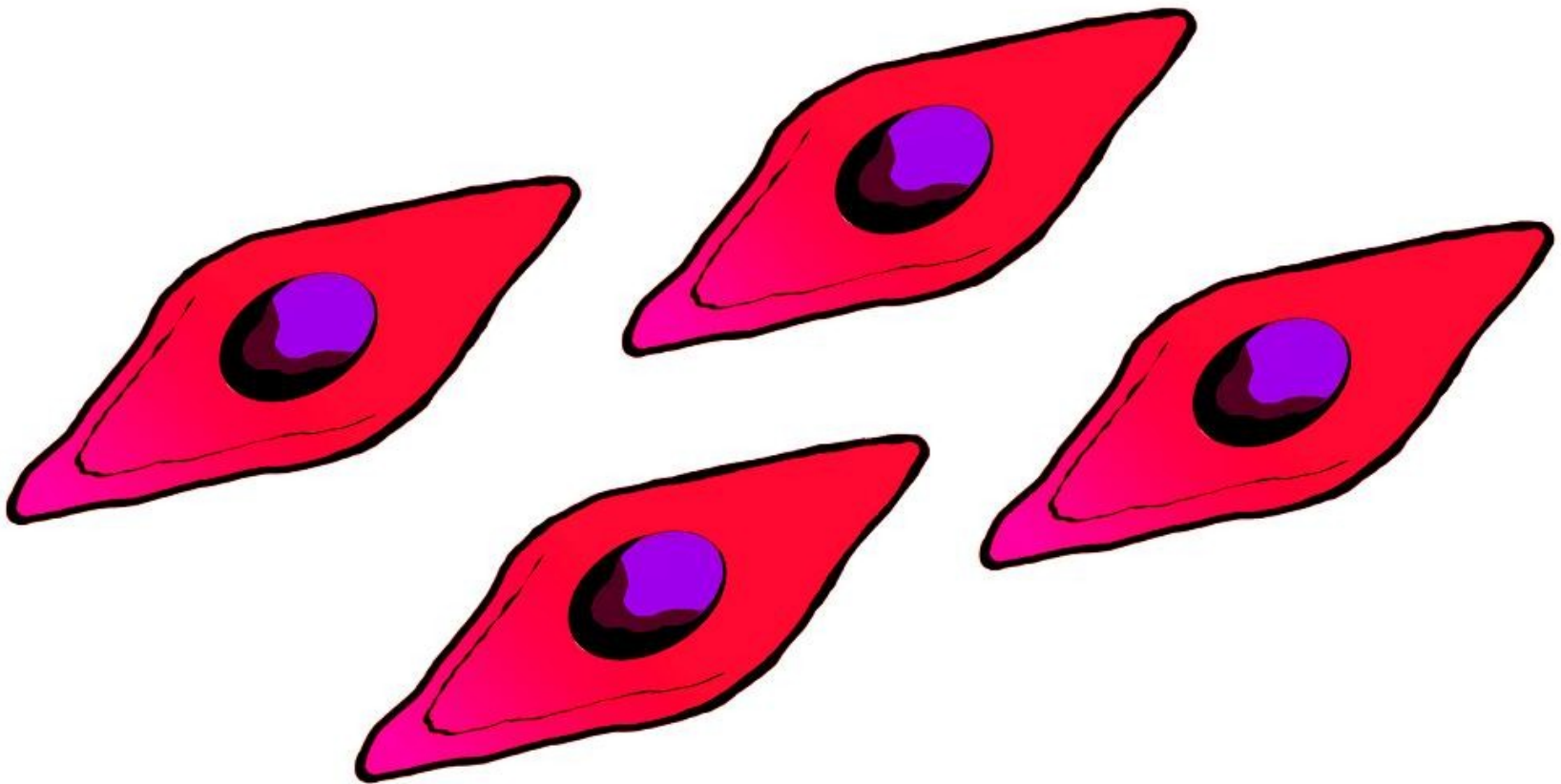
**Medical Director at MD Wellness**

1670 Route 34 N. 3R Floor Suite 3B Wall, NJ 07727

# Epithelial Cells



# Mesenchymal Cells






# Epithelial Cells

 Tight junction

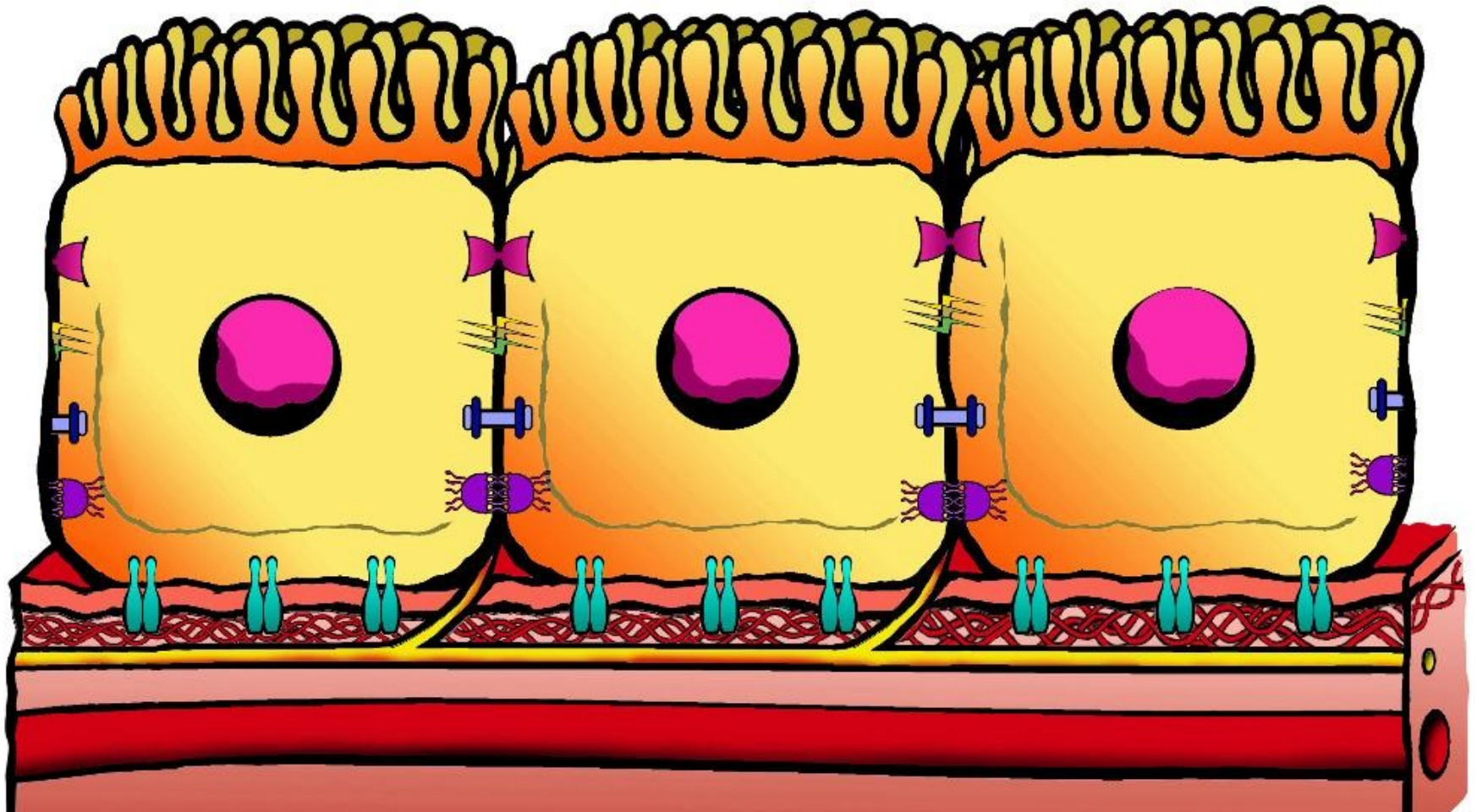
 Desmosome

 E-cadherin

 Basement Membrane

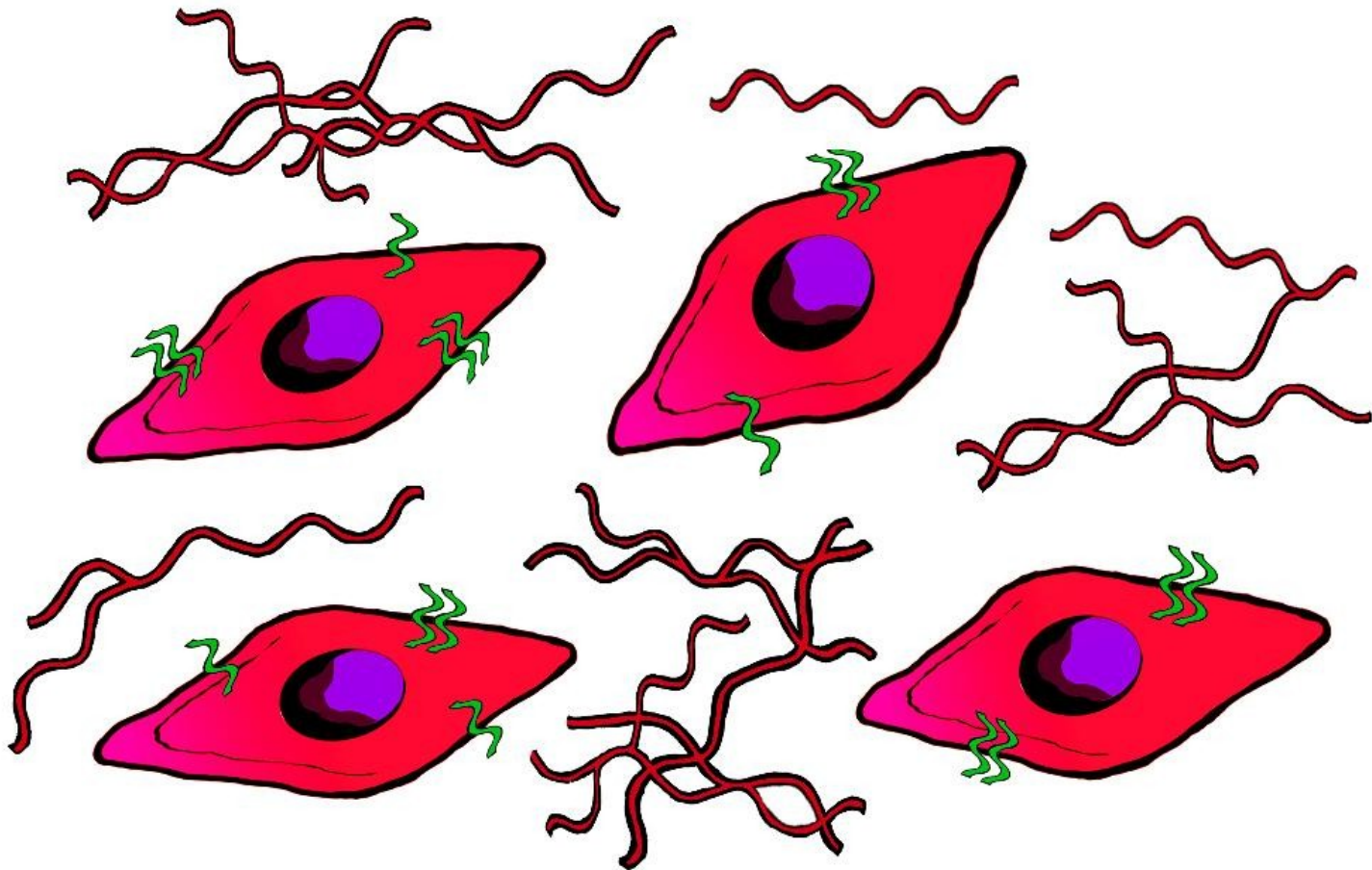
 Gap junction

 Integrin

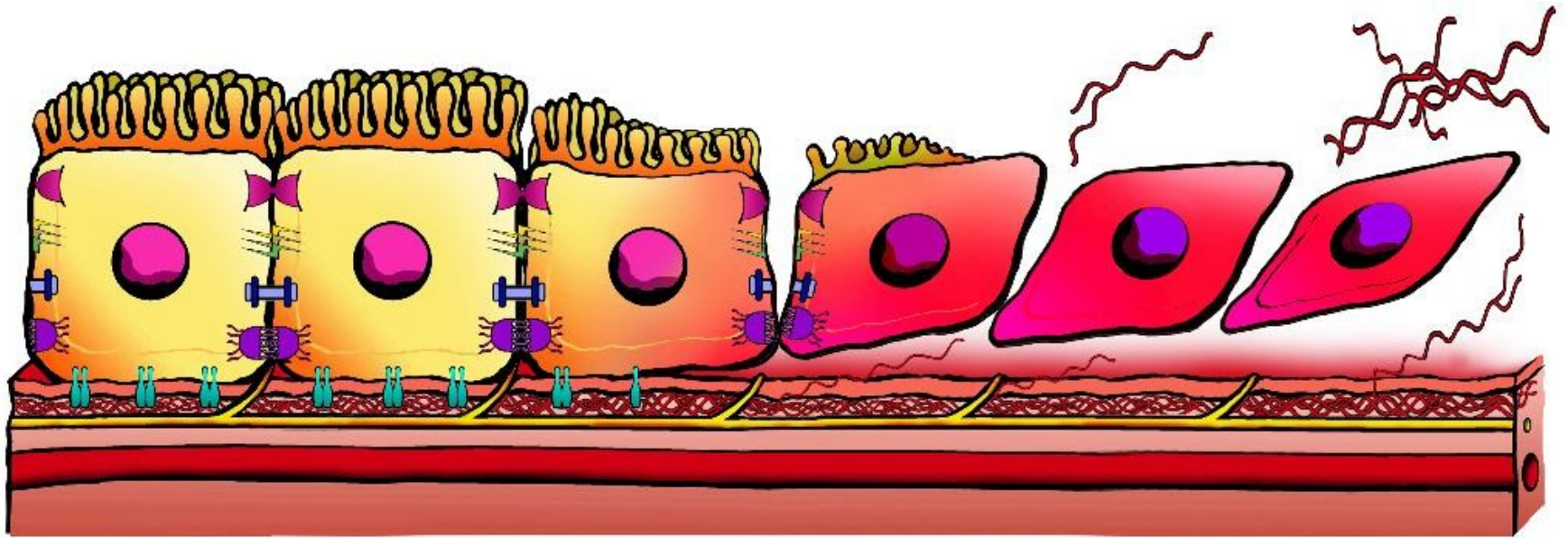


# Mesenchymal Cells

Calporin	FSP-1
Fibronectin	Vimatin
N-cadherin	$\alpha$ -SMA



# Transition from Epithelial to Mesenchymal

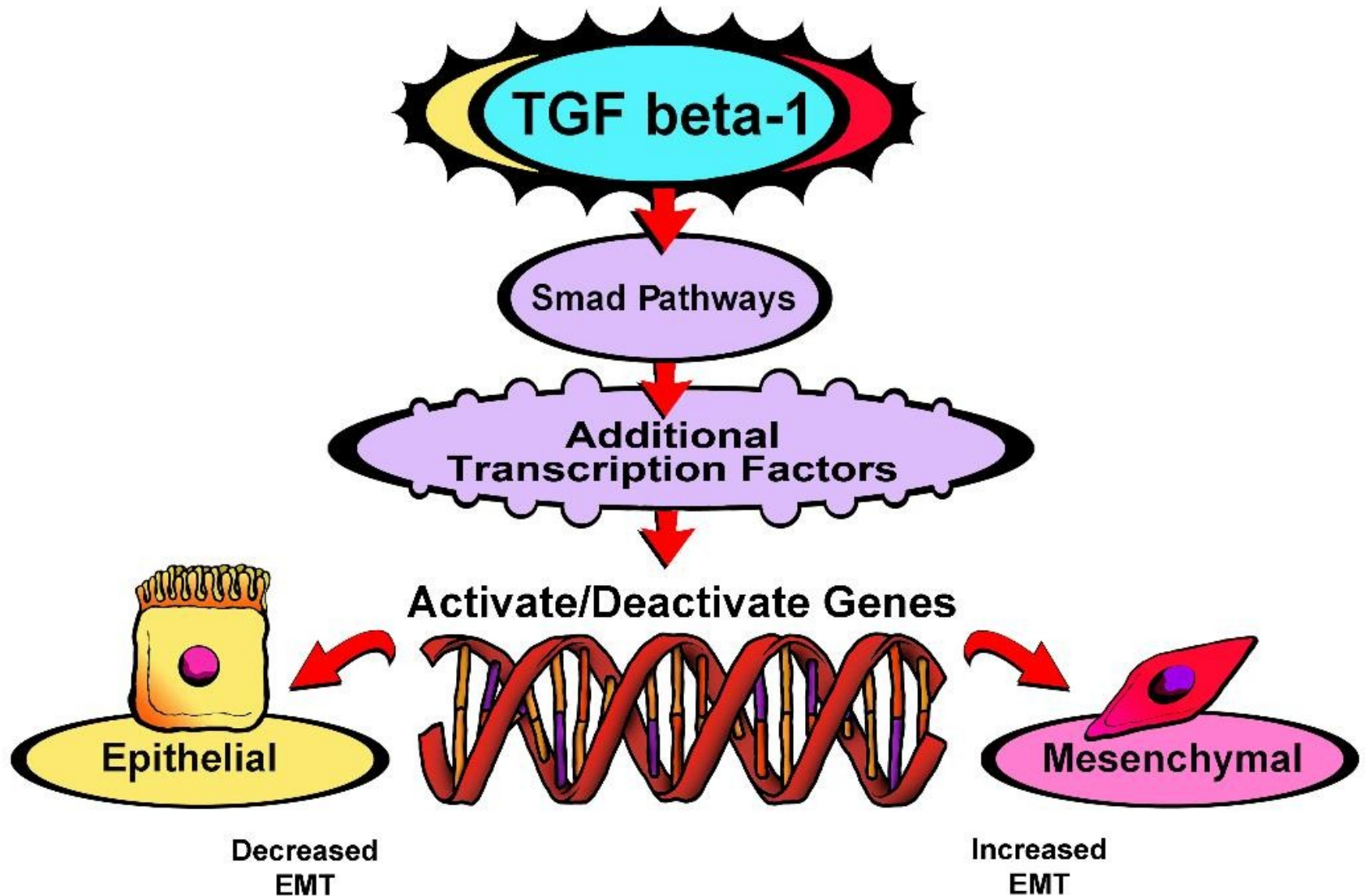


**Epithelial**

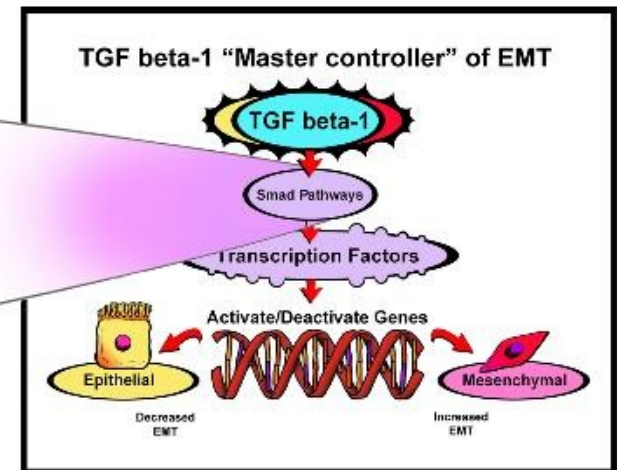
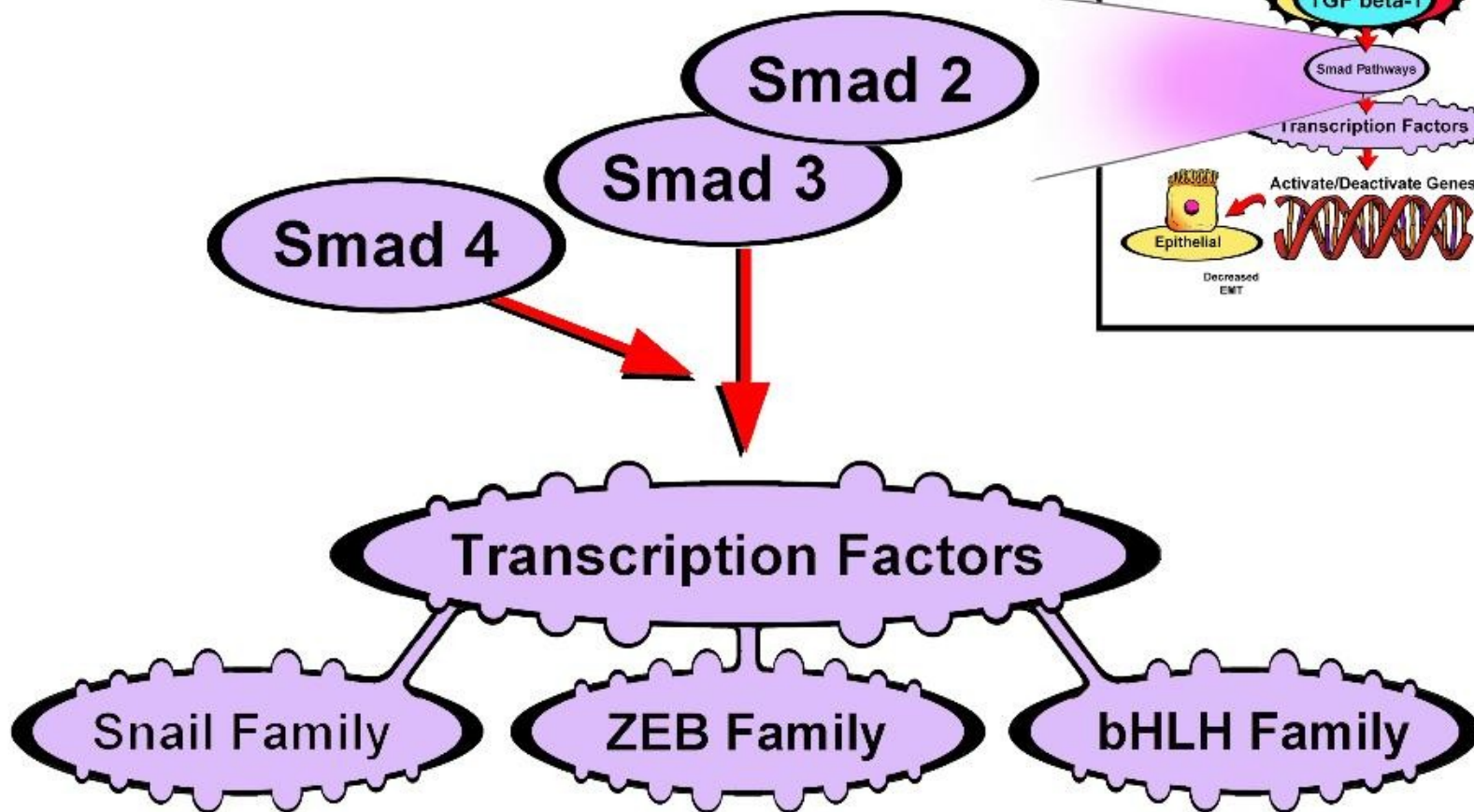
**Mesenchymal**



# TGF beta-1 “Master controller” of EMT

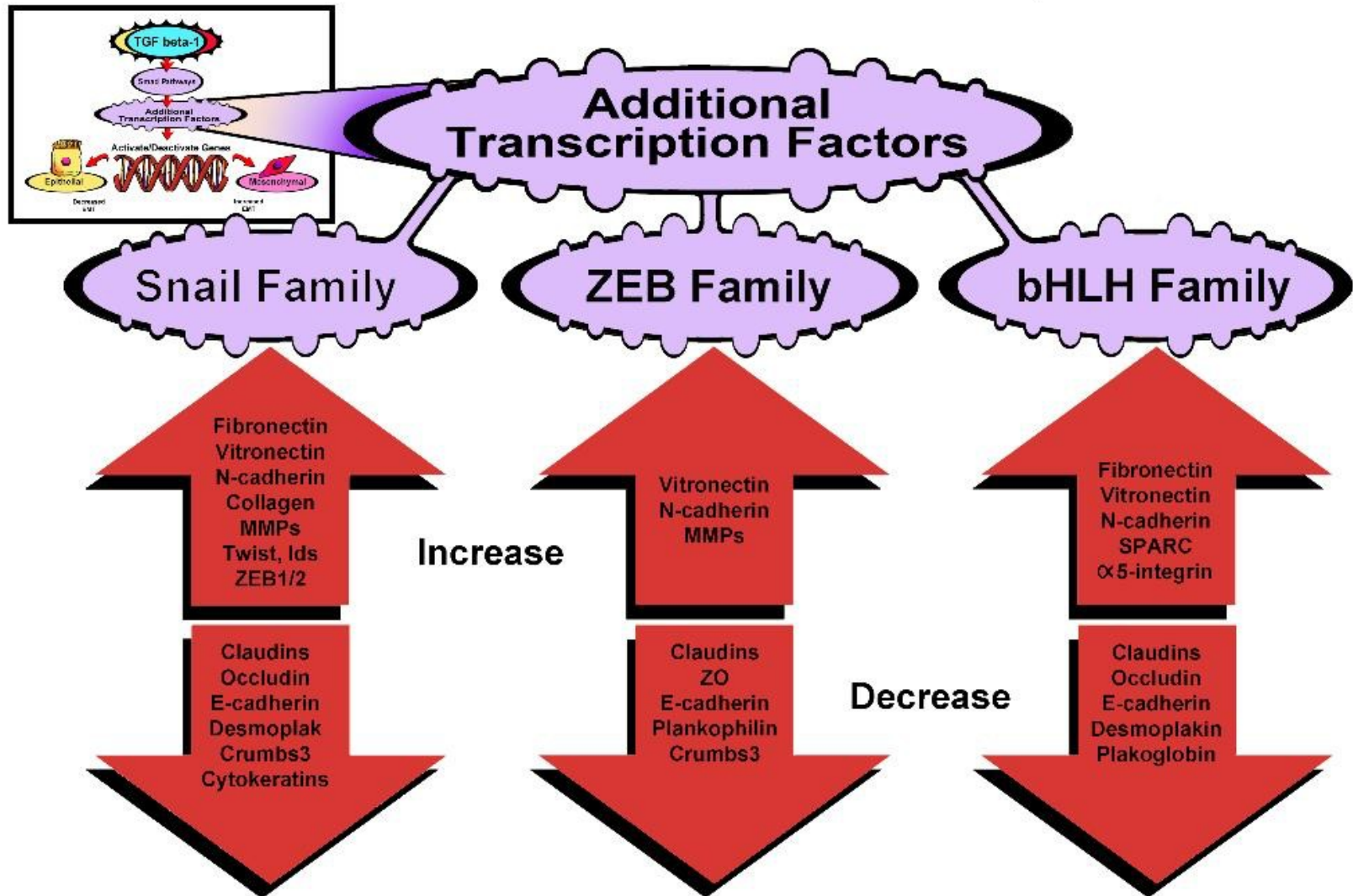


# Smad Pathway

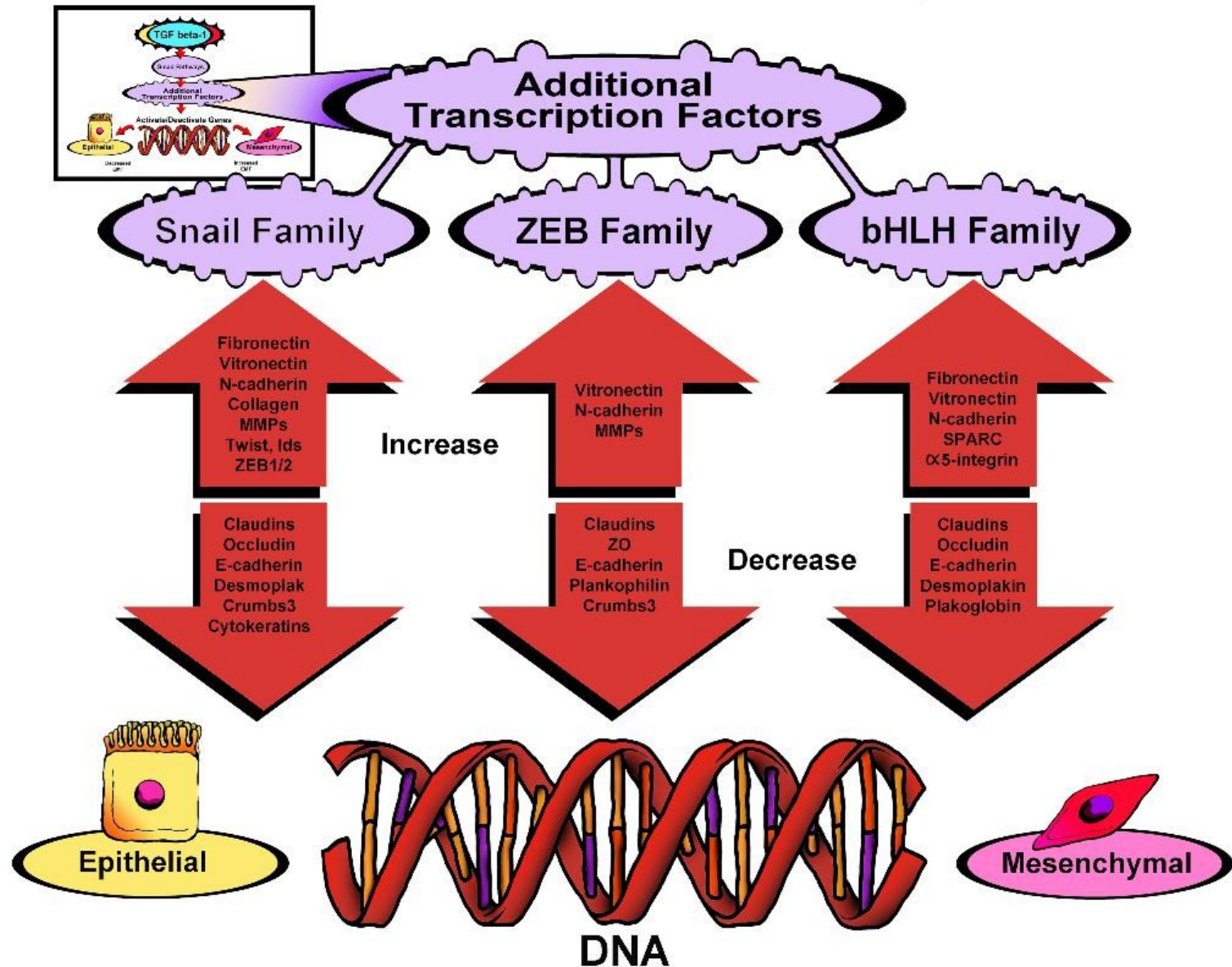




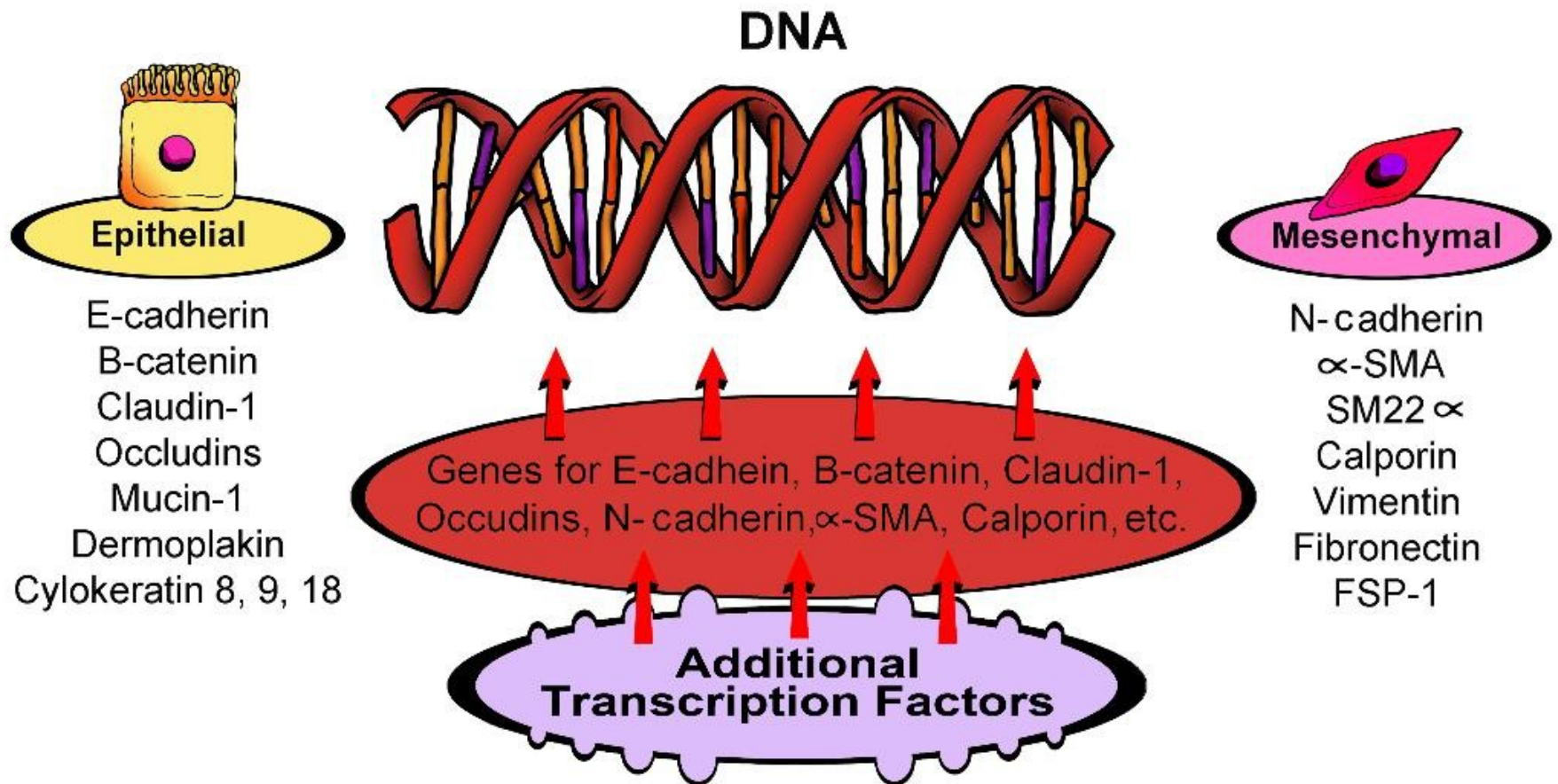
# The Three Main Families of Transcription Factors



# The Three Main Families of Transcription Factors

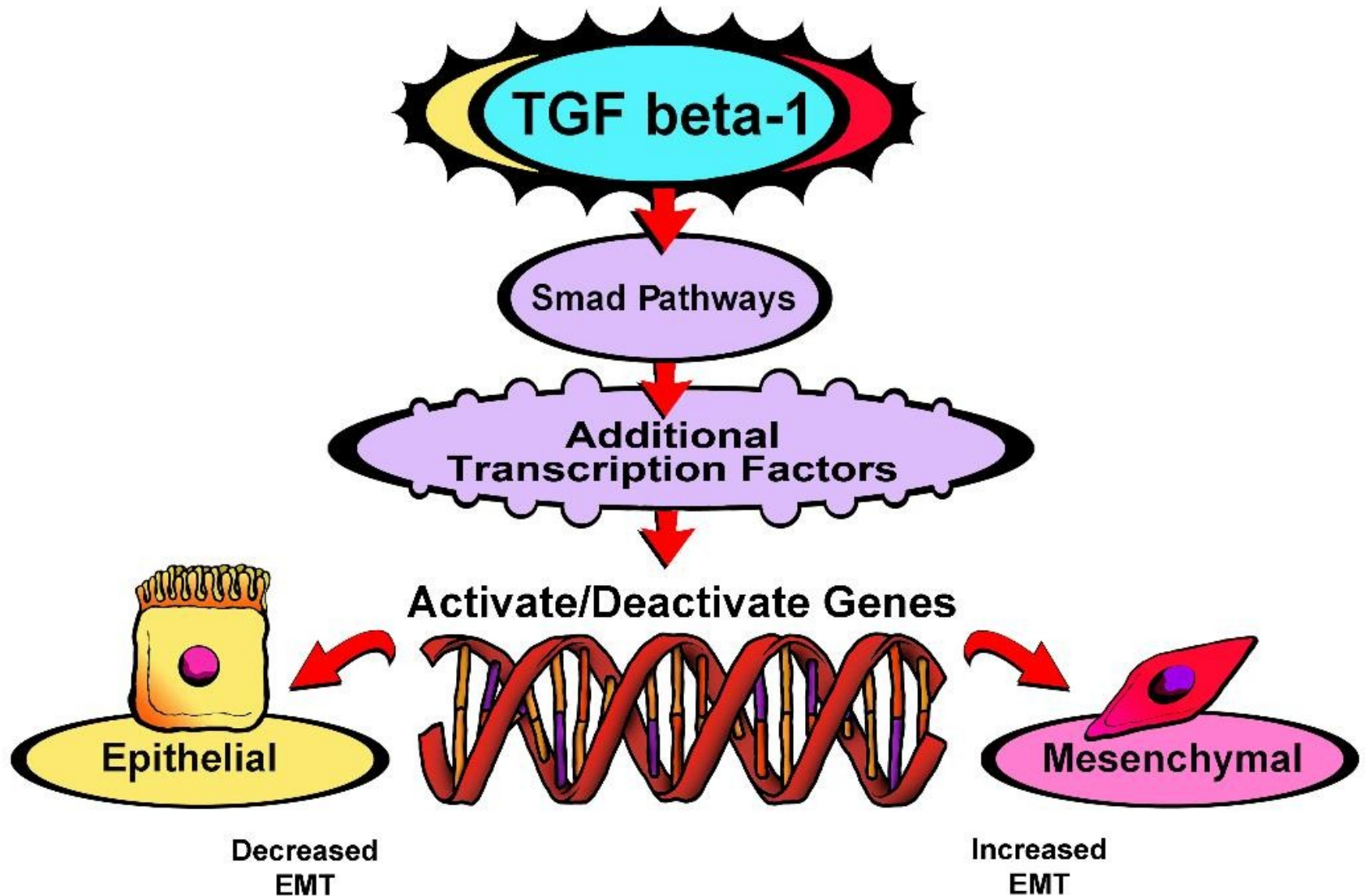


# Transcription Factors Control Genomics Which Control Proteinomics

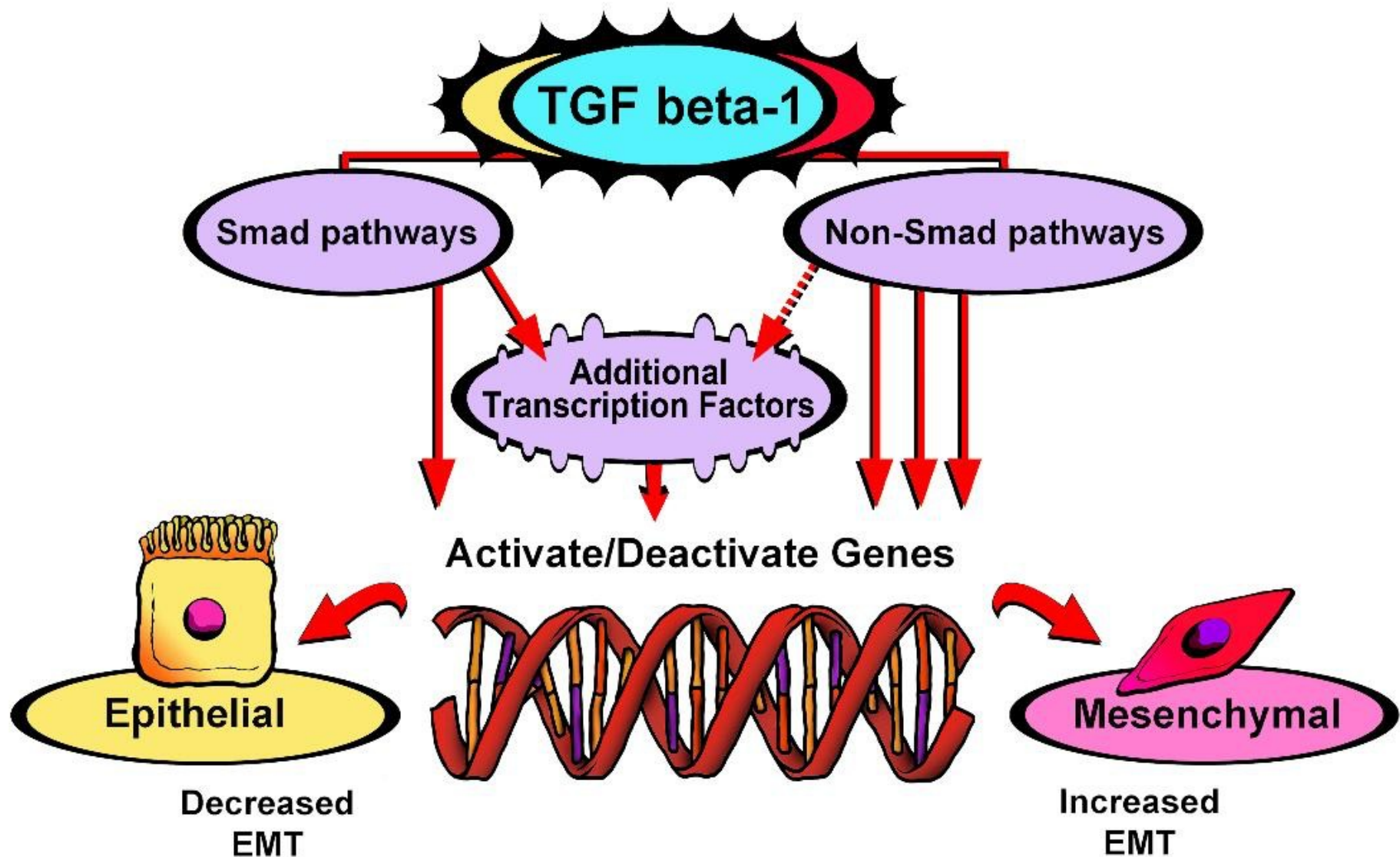




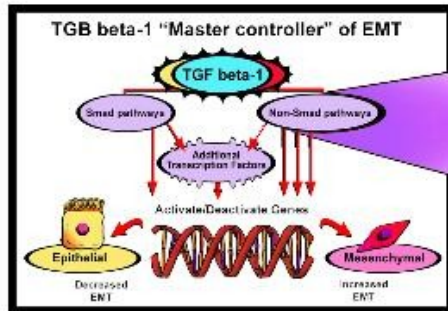
# TGF beta-1 “Master controller” of EMT



# TGF beta-1 “Master controller” of EMT



# Non-Smad Pathways



Degradation  
of tight  
junctions

Depolymerize  
Actin



↑ Fibronectin  
↑ Vimentin  
↑  $\alpha$ -SMA

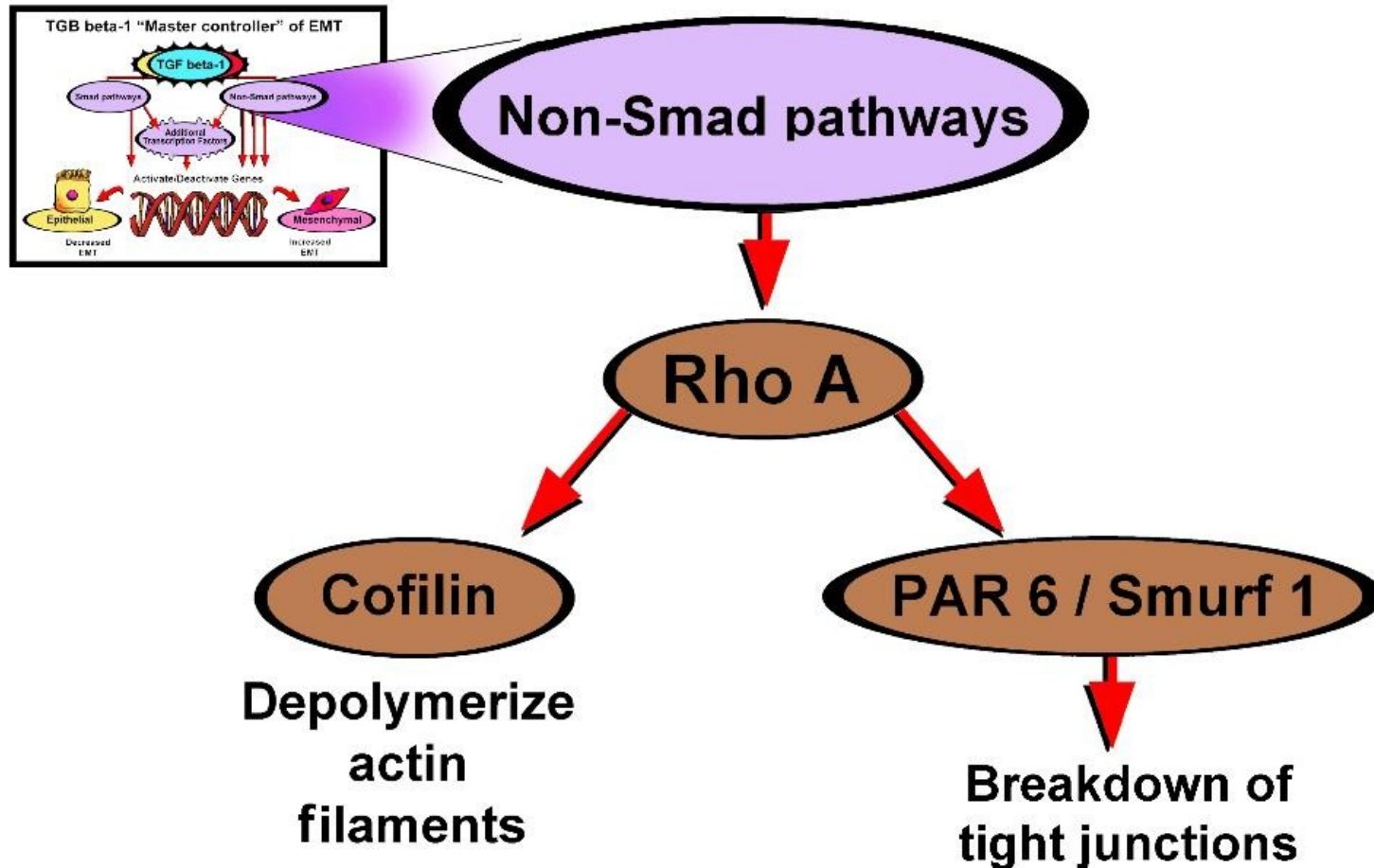
↓ E-cadherin



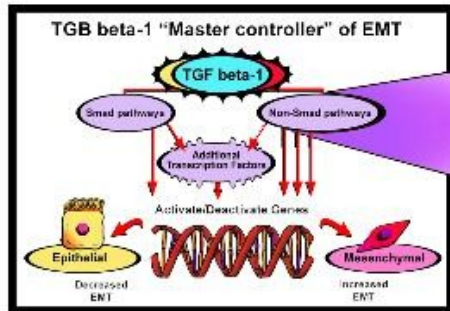
↑ Protein Synthesis  
↑ Cell size



# Non-Smad Pathways - Rho A



# Non-Smad Pathways



Degradation  
of tight  
junctions

Depolymerize  
Actin



↑ Fibronectin  
↑ Vimentin  
↑  $\alpha$ -SMA

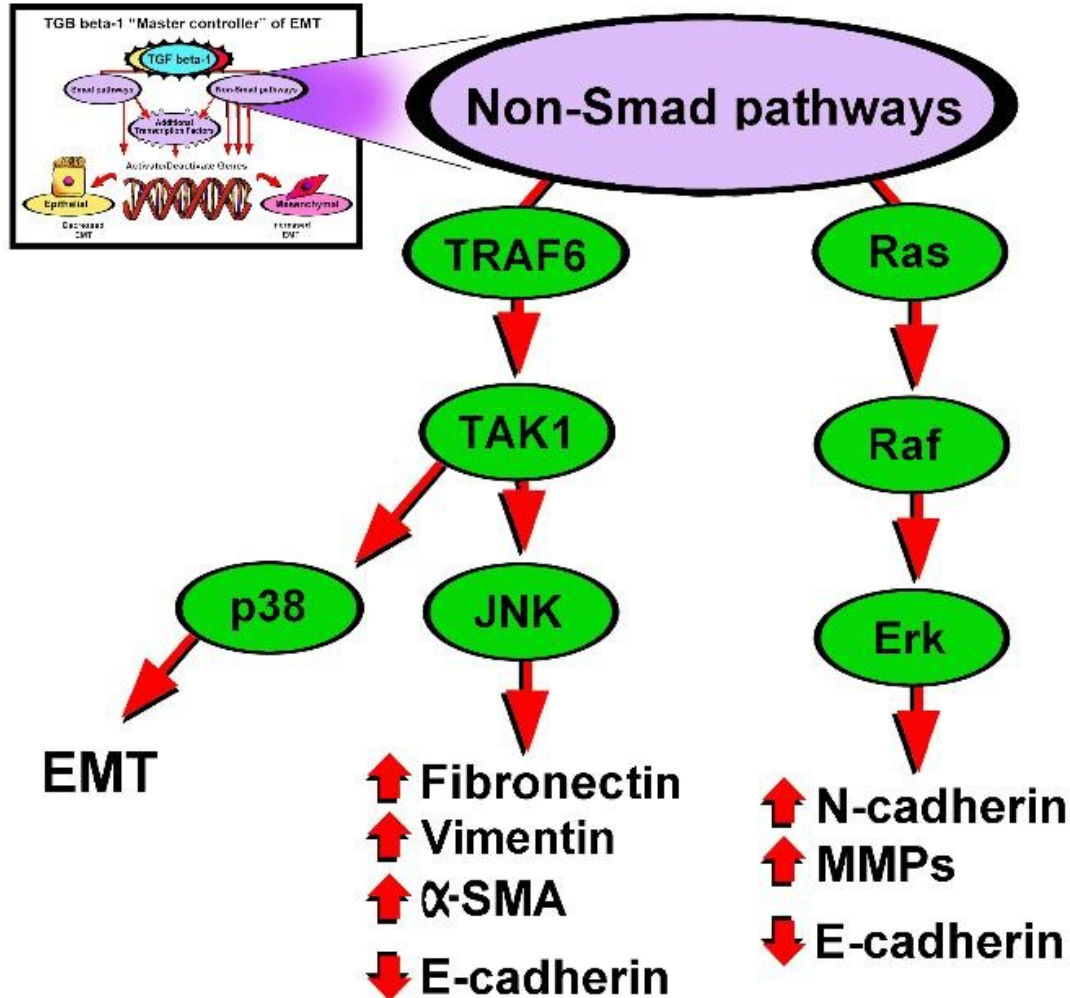
↓ E-cadherin



↑ Protein Synthesis  
↑ Cell size

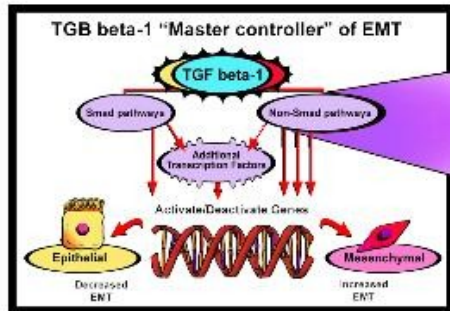
# Non-Smad Pathway

## Ras and MAP kinase





# Non-Smad Pathways



## Non-Smad pathways

Rho A

Degradation  
of tight  
junctions

Depolymerize  
Actin

Ras-Erk MAP kinase

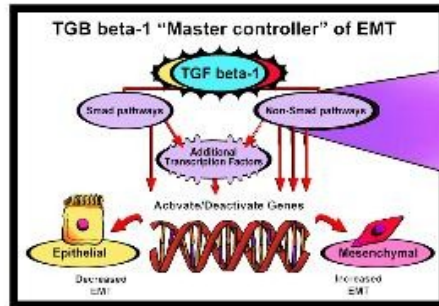
↑ Fibronectin  
↑ Vimentin  
↑  $\alpha$ -SMA

↓ E-cadherin

PI3 kinase

↑ Protein Synthesis  
↑ Cell size

# Non-Smad Pathway - PI3K



Non-Smad pathways

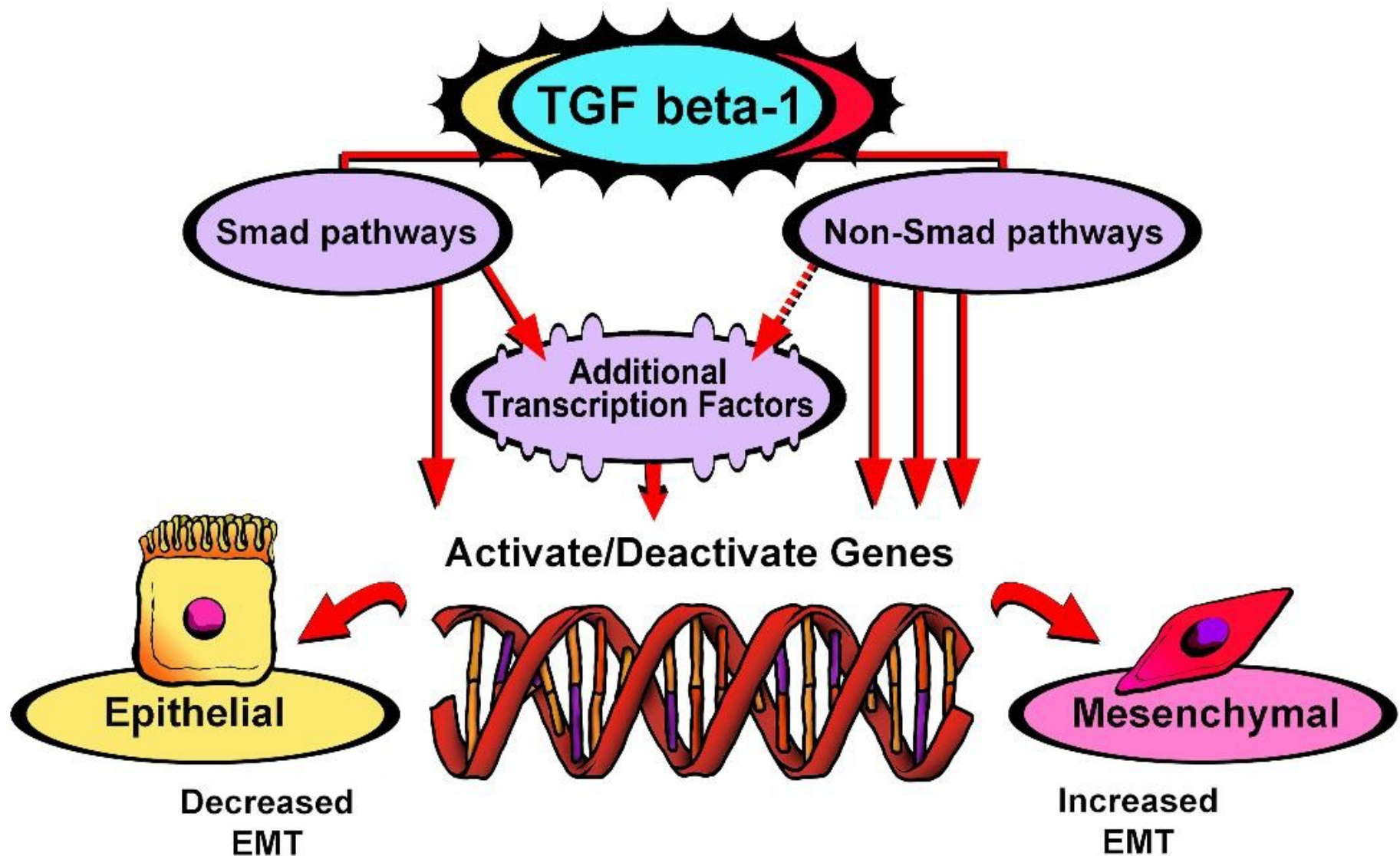
PI3K

AKT

MTOR

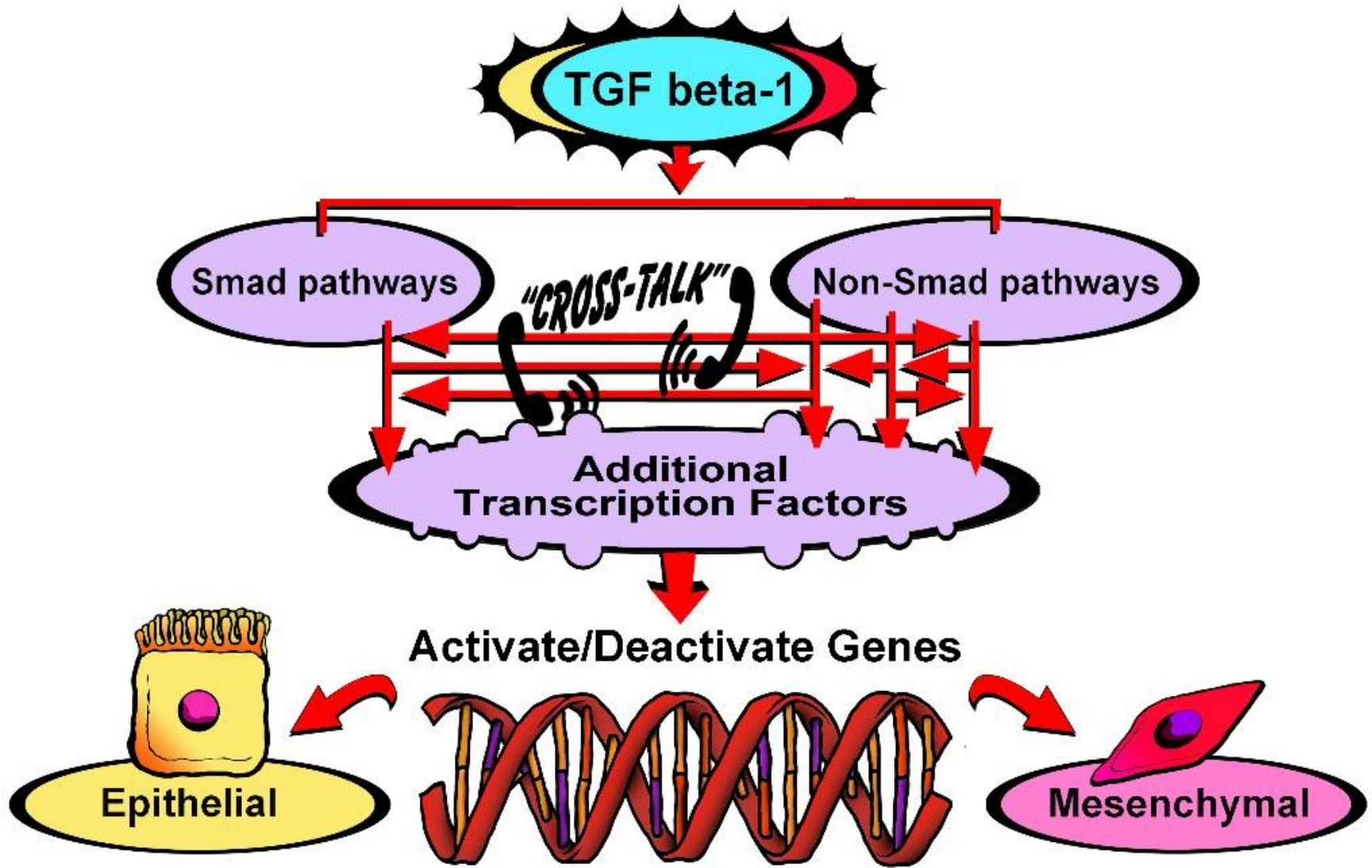
↑ Protein Synthesis  
↑ Cell size

# TGF beta-1 “Master controller” of EMT

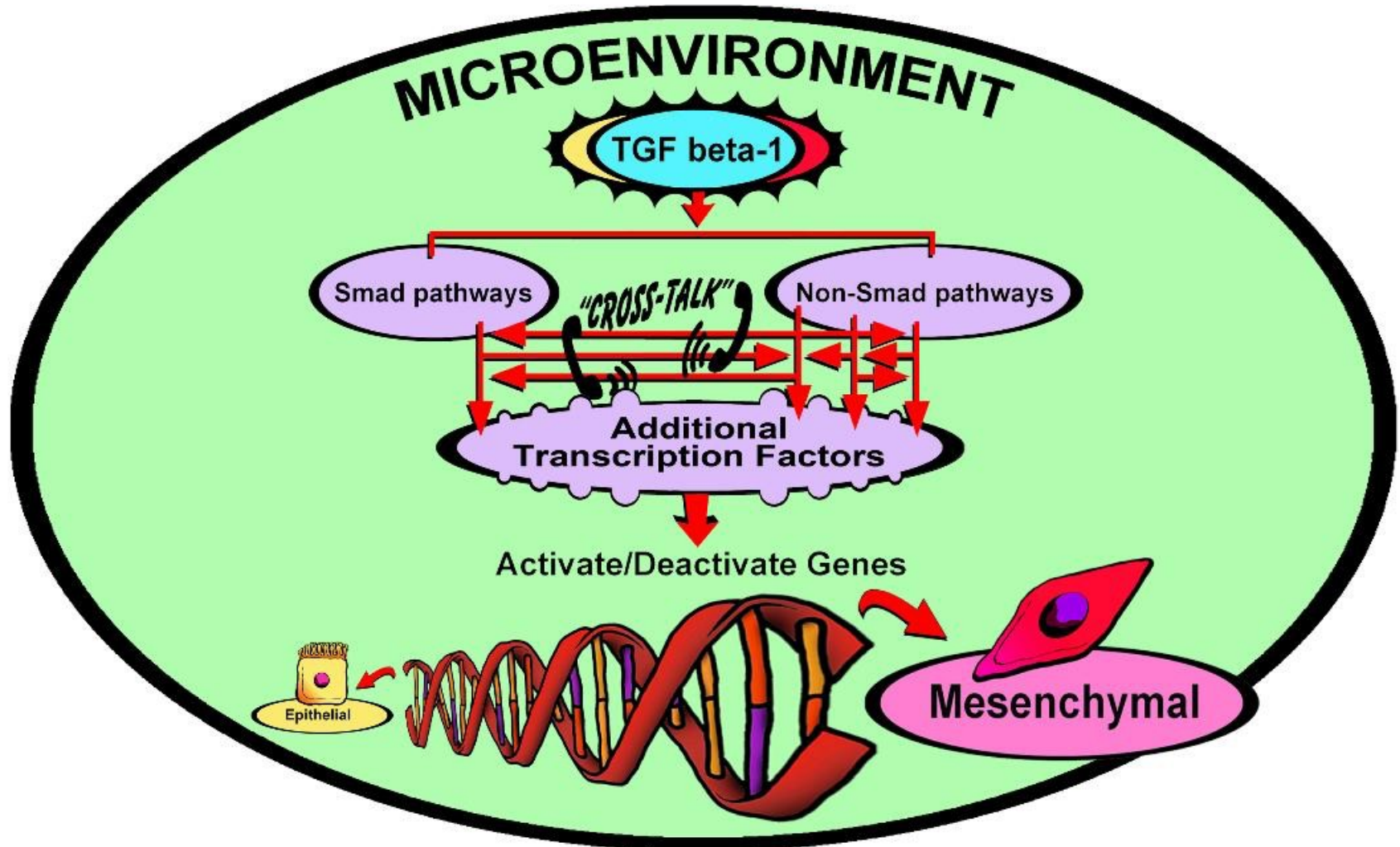




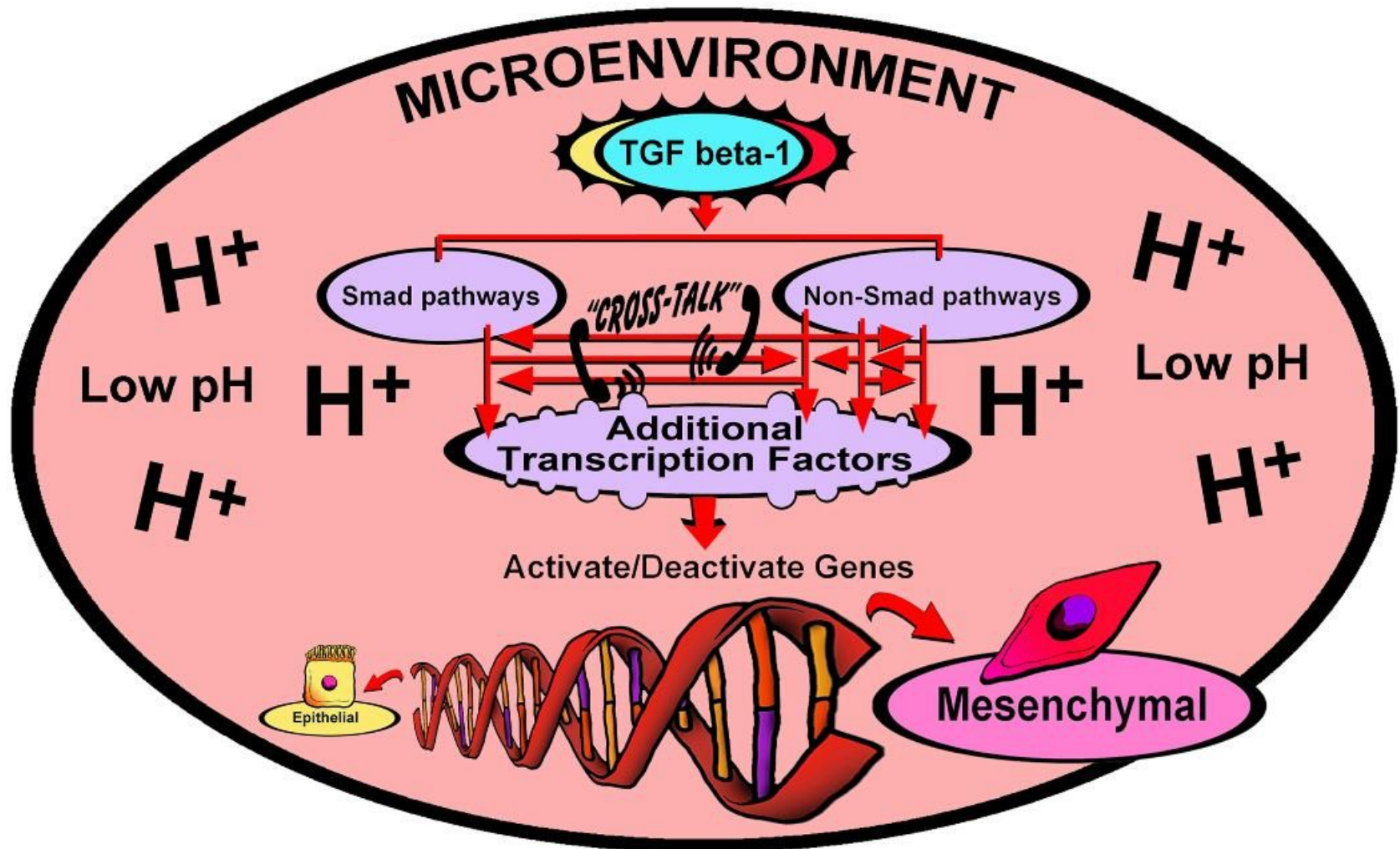
# “Cross Talk”



# Effects of Microenvironment on EMT

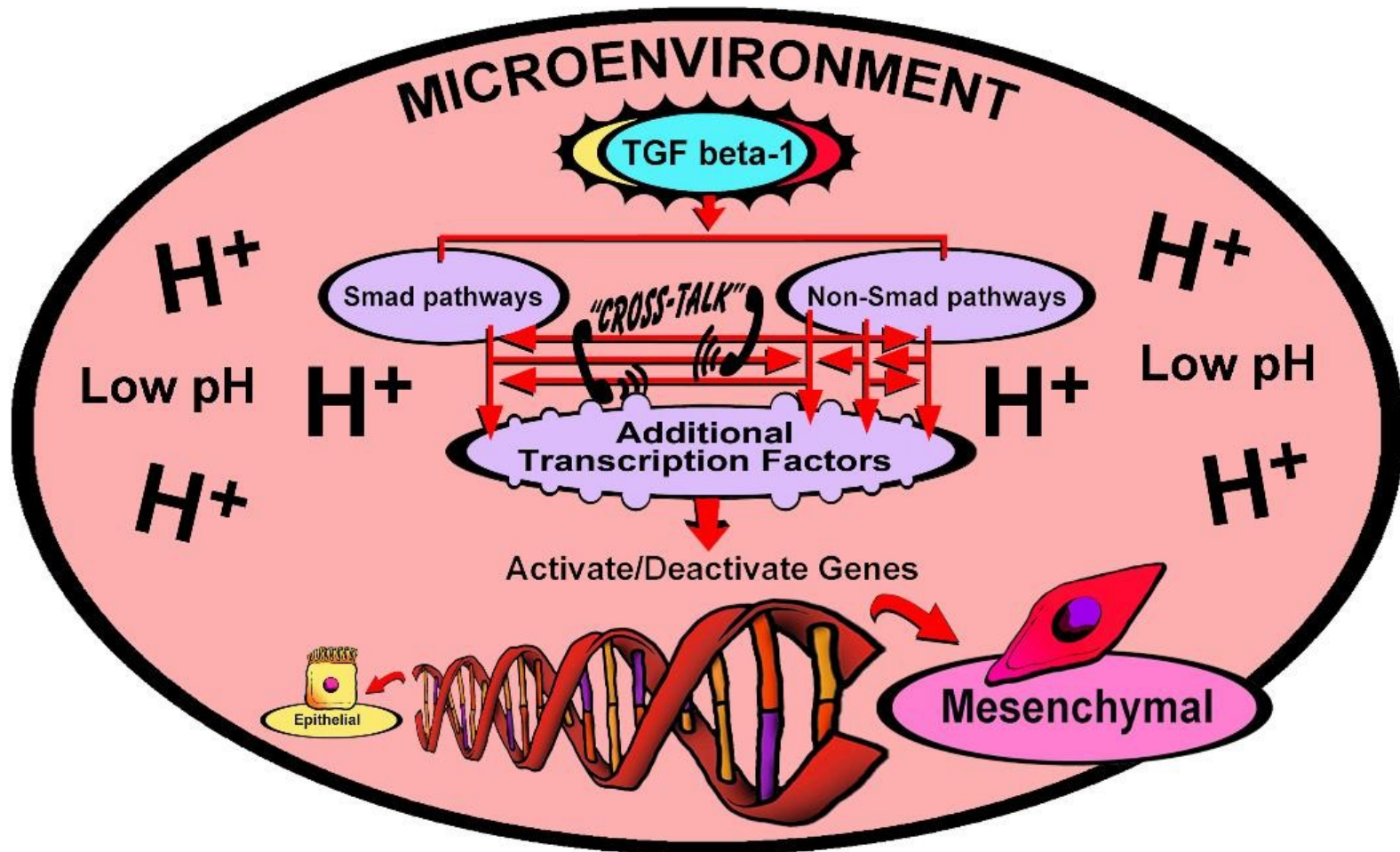


# Effect of Low pH Environment on EMT



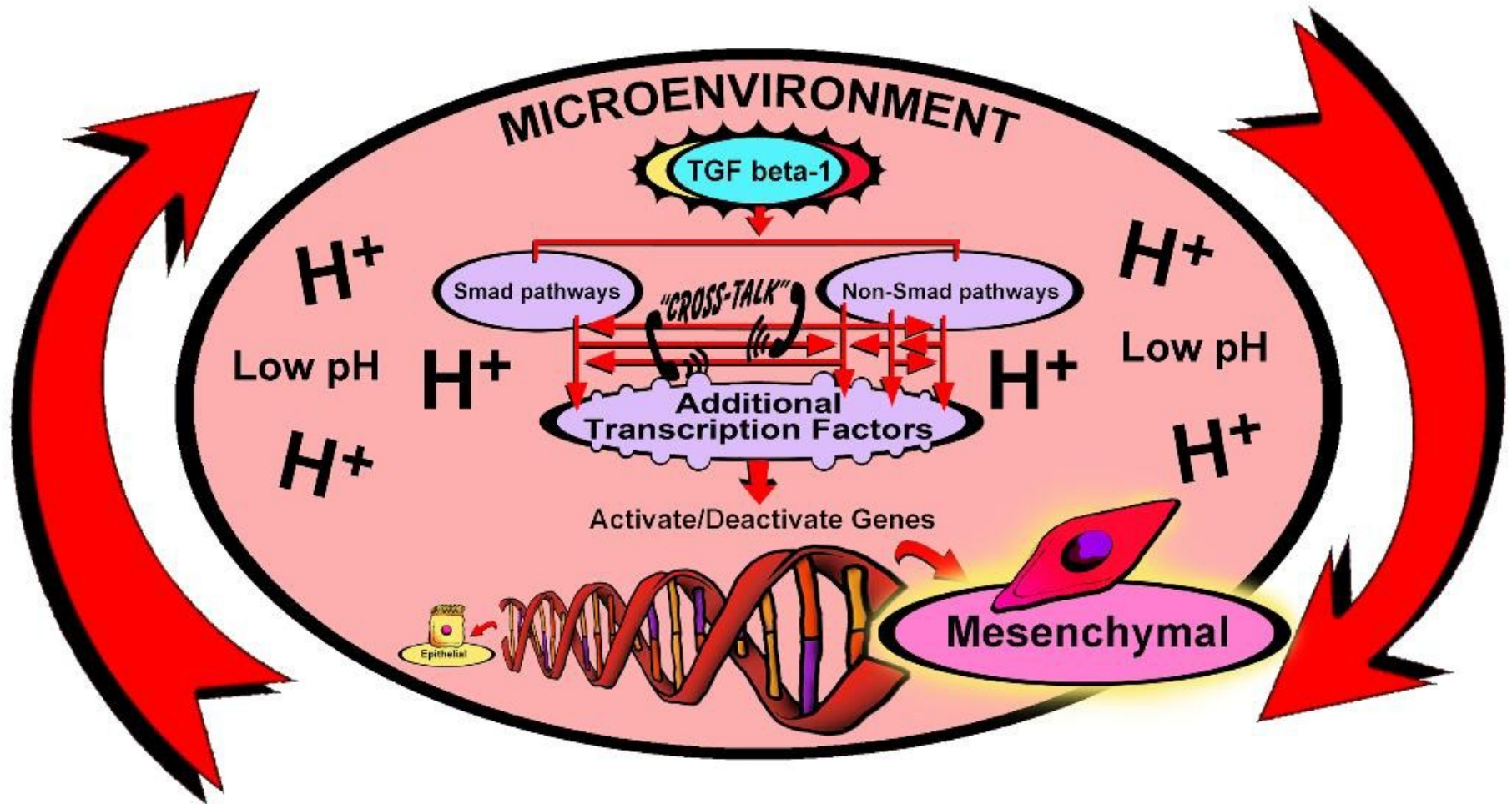


# The Effect of Anerobic Metabolism (AKA the Warburg Effect) on the Microenvironment and EMT



**Confirms Revici's Observations**

# The Viscious Cycle



# References



- **Non Smad Pathways and Cross-Talk**
- 
- **Non-Smad TGF-beta signals.**  
Moustakas A, Heldin CH.  
J Cell Sci. 2005 Aug 15;118(Pt 16):3573-84. Review.
- **Two major Smad pathways in TGF-beta superfamily signalling.** Miyazawa K, Shinozaki M, Hara T, Furuya T, Miyazono K. Genes Cells. 2002 Dec;7(12):1191-204. Review.
- **Crossing Smads.**  
Wrana JL.  
Sci STKE. 2000 Mar 14;2000(23):re1. Review.
- **Crosstalk mechanisms between the mitogen-activated protein kinase pathways and Smad signaling downstream of TGF-beta: implications for carcinogenesis.**  
Javelaud D, Mauviel A.  
Oncogene. 2005 Aug 29;24(37):5742-50. Review.
- **Regulation of TGF-beta signaling by Smad7.**  
Yan X, Liu Z, Chen Y.  
Acta Biochim Biophys Sin (Shanghai). 2009 Apr;41(4):263-72. Review.
- **Smad-dependent and Smad-independent pathways in TGF-beta family signalling.** Derynck R, Zhang YE.  
Nature. 2003 Oct 9;425(6958):577-84. Review.

- **New regulatory mechanisms of TGF-beta receptor function.**  
Kang JS, Liu C, Derynck R.  
Trends Cell Biol. 2009 Aug;19(8):385-94. doi: 10.1016/j.tcb.2009.05.008.  
Epub 2009 Aug 3. Review.
- **Regulation of Smad signalling by protein associations and signalling crosstalk.** Zhang Y, Derynck R.  
Trends Cell Biol. 1999 Jul;9(7):274-9. Review.
- **Integration of the TGF-beta pathway into the cellular signalling network.**  
Lutz M, Knaus P.  
Cell Signal. 2002 Dec;14(12):977-88. Review.
- **Transforming growth factor-beta and Smad signalling in kidney diseases.** Wang W, Koka V, Lan HY.  
Nephrology (Carlton). 2005 Feb;10(1):48-56. Review.
- **TGF-beta signalling from cell membrane to nucleus through SMAD proteins.** Heldin CH, Miyazono K, ten Dijke P.  
Nature. 1997 Dec 4;390(6659):465-71. Review.
- **Transforming growth factor beta signaling via Ras in mesenchymal cells requires p21-activated kinase 2 for extracellular signal-regulated kinase-dependent transcriptional responses.**  
Suzuki K, Wilkes MC, Garamszegi N, Edens M, Leof EB.  
Cancer Res. 2007 Apr 15;67(8):3673-82.
- **Transforming growth factor-beta signaling in cancer.** Rich J, Borton A, Wang X.  
Microsc Res Tech. 2001 Feb 15;52(4):363-73. Review.

- **Novel permissive role of epidermal growth factor in transforming growth factor beta (TGF-beta) signaling and growth suppression. Mediation by stabilization of TGF-beta receptor type II.**  
Song K, Krebs TL, Danielpour D.  
J Biol Chem. 2006 Mar 24;281(12):7765-74. Epub 2006 Jan 20.
- **Role of Smad proteins in the regulation of NF-kappaB by TGF-beta in colon cancer cells.** Grau AM, Datta PK, Zi J, Halder SK, Beauchamp RD.  
Cell Signal. 2006 Jul;18(7):1041-50. Epub 2005 Nov 8.
- **Fine tuning and cross-talking of TGF-beta signal by inhibitory Smads.** Park SH.  
J Biochem Mol Biol. 2005 Jan 31;38(1):9-16. Review.
- **Mechanisms of TGF-beta signaling from cell membrane to the nucleus.** Shi Y, Massagué J.  
Cell. 2003 Jun 13;113(6):685-700. Review.



## Redox Signaling and Warburg Effect

- **Reciprocal regulation of TGF- $\beta$  and reactive oxygen species: A perverse cycle for fibrosis.** Liu RM, Desai LP.  
Redox Biol. 2015 Dec;6:565-77. doi: 10.1016/j.redox.2015.09.009. Epub 2015 Oct 10. Review.
- **TGF- $\beta$  signaling in tissue fibrosis: redox controls, target genes and therapeutic opportunities.** Samarakoon R, Overstreet JM, Higgins PJ.  
Cell Signal. 2013 Jan;25(1):264-8. doi: 10.1016/j.cellsig.2012.10.003. Epub 2012 Oct 11. Review.
- **Redox control of p53 in the transcriptional regulation of TGF- $\beta$ 1 target genes through SMAD cooperativity.** Overstreet JM, Samarakoon R, Meldrum KK, Higgins PJ.  
Cell Signal. 2014 Jul;26(7):1427-36. doi: 10.1016/j.cellsig.2014.02.017. Epub 2014 Mar 5.
- **Role of reactive oxygen species in TGF-beta1-induced mitogen-activated protein kinase activation and epithelial- mesenchymal transition in renal tubular epithelial cells.** Rhyu DY, Yang Y, Ha H, Lee GT, Song JS, Uh ST, Lee HB.  
J Am Soc Nephrol. 2005 Mar;16(3):667-75. Epub 2005 Jan 26.
- **Arctigenin suppresses transforming growth factor- $\beta$ 1-induced expression of monocyte chemoattractant protein-1 and the subsequent epithelial-mesenchymal transition through reactive oxygen species-dependent ERK/NF- $\kappa$ B signaling pathway in renal tubular epithelial cells.** Li A, Wang J, Zhu D, Zhang X, Pan R, Wang R.  
Free Radic Res. 2015;49(9):1095-113. doi: 10.3109/10715762.2015.1038258. Epub 2015 May 13.
- **NADPH oxidase-dependent redox signaling in TGF- $\beta$ -mediated fibrotic responses.** Jiang F, Liu GS, Dusting GJ, Chan EC.  
Redox Biol. 2014 Jan 20;2:267-72. doi: 10.1016/j.redox.2014.01.012. eCollection 2014. Review.

- **Metabolic reprogramming of cancer-associated fibroblasts by TGF- $\beta$  drives tumor growth: connecting TGF- $\beta$  signaling with "Warburg-like" cancer metabolism and L-lactate production.**  
Guido C, Whitaker-Menezes D, Capparelli C, Balliet R, Lin Z, Pestell RG, Howell A, Aquila S, Andò S, Martinez- Outschoorn U, Sotgia F, Lisanti MP.
- **Cell Cycle.** 2012 Aug 15;11(16):3019-35. doi: 10.4161/cc.21384. Epub 2012 Aug 9.
- **CTGF drives autophagy, glycolysis and senescence in cancer-associated fibroblasts via HIF1 activation, metabolically promoting tumor growth.**  
Capparelli C, Whitaker-Menezes D, Guido C, Balliet R, Pestell TG, Howell A, Sneddon S, Pestell RG, Martinez- Outschoorn U, Lisanti MP, Sotgia F.
- **Cell Cycle.** 2012 Jun 15;11(12):2272-84. doi: 10.4161/cc.20717. Epub 2012 Jun 15.
- **Pyruvate kinase expression (PKM1 and PKM2) in cancer-associated fibroblasts drives stromal nutrient production and tumor growth.**  
Chiavarina B, Whitaker-Menezes D, Martinez-Outschoorn UE, Witkiewicz AK, Birbe R, Howell A, Pestell RG, Smith J, Daniel R, Sotgia F, Lisanti MP.
- **Cancer Biol Ther.** 2011 Dec 15;12(12):1101-13. doi: 10.4161/cbt.12.12.18703. Epub 2011 Dec 15.
- **Mitochondrial oxidative stress in cancer-associated fibroblasts drives lactate production, promoting breast cancer tumor growth: understanding the aging and cancer connection.**  
Balliet RM, Capparelli C, Guido C, Pestell TG, Martinez-Outschoorn UE, Lin Z, Whitaker-Menezes D, Chiavarina B, Pestell RG, Howell A, Sotgia F, Lisanti MP.
- **Cell Cycle.** 2011 Dec 1;10(23):4065-73. doi: 10.4161/cc.10.23.18254. Epub 2011 Dec 1.
- **Tumor microenvironment and metabolic synergy in breast cancers: critical importance of mitochondrial fuels and function.**  
Martinez-Outschoorn U, Sotgia F, Lisanti MP.  
**Semin Oncol.** 2014 Apr;41(2):195-216. doi: 10.1053/j.seminoncol.2014.03.002. Epub 2014 Mar 5. Review.
- **Lactic acid is elevated in idiopathic pulmonary fibrosis and induces myofibroblast differentiation via pH- dependent activation of transforming growth factor- $\beta$ .**
- **Kottmann RM, Kulkarni AA, Smolnycki KA, Lyda E, Dahanayake T, Salibi R, Honnons S, Jones C, Isern NG, Hu JZ, Nathan SD, Grant G, Phipps RP, Sime PJ.**
- **Am J Respir Crit Care Med.** 2012 Oct 15;186(8):740-51. doi: 10.1164/rccm.201201-0084OC. Epub 2012 Aug 23.

- **Smad Pathways and Transcription factors**
- 
- **TGF-beta and epithelial-to-mesenchymal transitions.** Zavadil J, Böttinger EP. *Oncogene*. 2005 Aug 29;24(37):5764-74. Review.
- **Integration of TGF-beta/Smad and Jagged1/Notch signalling in epithelial-to-mesenchymal transition.** Zavadil J, Cermak L, Soto-Nieves N, Böttinger EP. *EMBO J*. 2004 Mar 10;23(5):1155-65. Epub 2004 Feb 19.
- **TGF- $\beta$  induces sustained upregulation of SNAI1 and SNAI2 through Smad and non-Smad pathways in a human corneal epithelial cell line.**  
Aomatsu K, Arao T, Sugioka K, Matsumoto K, Tamura D, Kudo K, Kaneda H, Tanaka K, Fujita Y, Shimomura Y, Nishio K.
- **Invest Ophthalmol Vis Sci.** 2011 Apr 14;52(5):2437-43. doi: 10.1167/iovs.10-5635.
- **Snail is required for transforming growth factor-beta-induced epithelial-mesenchymal transition by activating PI3 kinase/Akt signal pathway.**  
Cho HJ, Baek KE, Saika S, Jeong MJ, Yoo J. *Biochem Biophys Res Commun*. 2007 Feb 9;353(2):337-43. Epub 2006 Dec 14.
- **Transforming growth factor-beta employs HMGA2 to elicit epithelial-mesenchymal transition.**  
Thuault S, Valcourt U, Petersen M, Manfioletti G, Heldin CH, Moustakas A. *J Cell Biol*. 2006 Jul 17;174(2):175-83. Epub 2006 Jul 10.
- **Transforming growth factor-beta signaling through the Smad pathway: role in extracellular matrix gene expression and regulation.**  
Verrecchia F, Mauviel A. *J Invest Dermatol*. 2002 Feb;118(2):211-5. Review.
- **Excessive hyaluronan production promotes acquisition of cancer stem cell signatures through the coordinated regulation of Twist and the transforming growth factor  $\beta$  (TGF- $\beta$ )-Snail signaling axis.**  
Chanmee T, Ontong P, Mochizuki N, Kongtawelert P, Konno K, Itano N. *J Biol Chem*. 2014 Sep 19;289(38):26038-56. doi: 10.1074/jbc.M114.564120. Epub 2014 Jul 30.
- **TGF-beta-induced epithelial to mesenchymal transition.**  
Xu J, Lamouille S, Derynck R. *Cell Res*. 2009 Feb;19(2):156-72. doi: 10.1038/cr.2009.5. Review.



- Transforming growth factor-beta signaling in epithelial-mesenchymal transition and progression of cancer. Miyazono K.  
Proc Jpn Acad Ser B Phys Biol Sci. 2009;85(8):314-23. Review.
- Integrin beta 1 signaling is necessary for transforming growth factor-beta activation of p38MAPK and epithelial plasticity.  
Bhowmick NA, Zent R, Ghiassi M, McDonnell M, Moses HL.  
J Biol Chem. 2001 Dec 14;276(50):46707-13. Epub 2001 Oct 5.
- Genetic programs of epithelial cell plasticity directed by transforming growth factor-beta. Zavadil J, Bitzer M, Liang D, Yang YC, Massimi A, Kneitz S, Piek E, Bottinger EP.  
Proc Natl Acad Sci U S A. 2001 Jun 5;98(12):6686-91.
- Role of reactive oxygen species in TGF-beta1-induced mitogen-activated protein kinase activation and epithelial- mesenchymal transition in renal tubular epithelial cells.  
Rhyu DY, Yang Y, Ha H, Lee GT, Song JS, Uh ST, Lee HB.  
J Am Soc Nephrol. 2005 Mar;16(3):667-75. Epub 2005 Jan 26.
- Induction by transforming growth factor-beta1 of epithelial to mesenchymal transition is a rare event in vitro. Brown KA, Aakre ME, Gorska AE, Price JO, Eltom SE, Pietenpol JA, Moses HL.  
Breast Cancer Res. 2004;6(3):R215-31. Epub 2004 Mar 17.
- Induction of an epithelial to mesenchymal transition in human immortal and malignant keratinocytes by TGF- beta1 involves MAPK, Smad and AP-1 signalling pathways.  
Davies M, Robinson M, Smith E, Huntley S, Prime S, Paterson I.  
J Cell Biochem. 2005 Aug 1;95(5):918-31.
- SIP1 (Smad interacting protein 1) and deltaEF1 (delta-crystallin enhancer binding factor) are structurally similar transcriptional repressors.  
van Grunsven LA, Schellens A, Huylebroeck D, Verschueren K.  
J Bone Joint Surg Am. 2001;83-A Suppl 1(Pt 1):S40-7. Review.
- Ras alters epithelial-mesenchymal transition in response to TGFbeta by reducing actin fibers and cell-matrix adhesion.  
Safina AF, Varga AE, Bianchi A, Zheng Q, Kunnev D, Liang P, Bakin AV.
- A novel mechanism by which hepatocyte growth factor blocks tubular epithelial to mesenchymal transition. Yang J, Dai C, Liu Y.  
J Am Soc Nephrol. 2005 Jan;16(1):68-78. Epub 2004 Nov 10.

- **Developmental expression of Smad1-7 suggests critical function of TGF-beta/BMP signaling in regulating epithelial-mesenchymal interaction during tooth morphogenesis.**  
Xu X, Jeong L, Han J, Ito Y, Bringas P Jr, Chai Y.  
Int J Dev Biol. 2003 Feb;47(1):31-9.
- **Id2 and Id3 define the potency of cell proliferation and differentiation responses to transforming growth factor beta and bone morphogenetic protein.**  
Kowanetz M, Valcourt U, Bergström R, Heldin CH, Moustakas A.  
Mol Cell Biol. 2004 May;24(10):4241-54.
- **Regulation of epithelial-mesenchymal transition in palatal fusion.**  
Yu W, Ruest LB, Svoboda KK.  
Exp Biol Med (Maywood). 2009 May;234(5):483-91. doi: 10.3181/0812-MR-365. Epub 2009 Feb 20. Review.
- **Src activation is not necessary for transforming growth factor (TGF)-beta-mediated epithelial to mesenchymal transitions (EMT) in mammary epithelial cells. PP1 directly inhibits TGF-beta receptors I and II.**  
Maeda M, Shintani Y, Wheelock MJ, Johnson KR.  
J Biol Chem. 2006 Jan 6;281(1):59-68. Epub 2005 Nov 1.
- **TGF-(beta) type I receptor/ALK-5 and Smad proteins mediate epithelial to mesenchymal transdifferentiation in NMuMG breast epithelial cells.**  
Piek E, Moustakas A, Kurisaki A, Heldin CH, ten Dijke P.  
J Cell Sci. 1999 Dec;112 ( Pt 24):4557-68.
- **Transforming growth factor-beta signaling during epithelial-mesenchymal transformation: implications for embryogenesis and tumor metastasis.**  
Nawshad A, Lagamba D, Polad A, Hay ED.  
Cells Tissues Organs. 2005;179(1-2):11-23. Review.
- **BMP-7 counteracts TGF-beta1-induced epithelial-to-mesenchymal transition and reverses chronic renal injury.** Zeisberg M, Hanai J, Sugimoto H, Mammoto T, Charytan D, Strutz F, Kalluri R.  
Nat Med. 2003 Jul;9(7):964-8.
- **Targeted disruption of TGF-beta1/Smad3 signaling protects against renal tubulointerstitial fibrosis induced by unilateral ureteral obstruction.**  
Sato M, Muragaki Y, Saika S, Roberts AB, Ooshima A.  
J Clin Invest. 2003 Nov;112(10):1486-94.

- Leaving the neighborhood: molecular mechanisms involved during epithelial-mesenchymal transition. Savagner P.  
Bioessays. 2001 Oct;23(10):912-23. Review.
- Smad3 signaling is required for epithelial-mesenchymal transition of lens epithelium after injury. Saika S, Kono-Saika S, Ohnishi Y, Sato M, Muragaki Y, Ooshima A, Flanders KC, Yoo J, Anzano M, Liu CY, Kao WW, Roberts AB.  
Am J Pathol. 2004 Feb;164(2):651-63.
- The epithelial mesenchymal transition confers resistance to the apoptotic effects of transforming growth factor Beta in fetal rat hepatocytes.  
Valdés F, Alvarez AM, Locascio A, Vega S, Herrera B, Fernández M, Benito M, Nieto MA, Fabregat I.  
Mol Cancer Res. 2002 Nov;1(1):68-78.
- Snail family members and cell survival in physiological and pathological cleft palates. Martínez-Alvarez C, Blanco MJ, Pérez R, Rabadán MA, Aparicio M, Resel E, Martínez T, Nieto MA. Dev Biol. 2004 Jan 1;265(1):207-18.
- Transforming growth factor beta-1 induces snail transcription factor in epithelial cell lines: mechanisms for epithelial mesenchymal transitions.  
Peinado H, Quintanilla M, Cano A.  
J Biol Chem. 2003 Jun 6;278(23):21113-23. Epub 2003 Mar 28.
- Epithelial to mesenchymal transition in Madin-Darby canine kidney cells is accompanied by down-regulation of Smad3 expression, leading to resistance to transforming growth factor-beta-induced growth arrest.  
Nicolás FJ, Lehmann K, Warne PH, Hill CS, Downward J.  
J Biol Chem. 2003 Jan 31;278(5):3251-6. Epub 2002 Nov 14.
- Dual roles of myocardin-related transcription factors in epithelial mesenchymal transition via slug induction and actin remodeling.  
Morita T, Mayanagi T, Sobue K.  
J Cell Biol. 2007 Dec 3;179(5):1027-42.
- Mechanisms of the epithelial-mesenchymal transition by TGF-beta. Wendt MK, Allington TM, Schiemann WP.  
Future Oncol. 2009 Oct;5(8):1145-68. doi: 10.2217/fon.09.90. Review.

- The pathophysiology of epithelial-mesenchymal transition induced by transforming growth factor-beta in normal and malignant mammary epithelial cells.
- Taylor MA, Parvani JG, Schiemann WP.
- J Mammary Gland Biol Neoplasia. 2010 Jun;15(2):169-90. doi: 10.1007/s10911-010-9181-1. Epub 2010 May 15. Review.
- Deconstructing the mechanisms and consequences of TGF- $\beta$ -induced EMT during cancer progression. Wendt MK, Tian M, Schiemann WP. Cell Tissue Res. 2012 Jan;347(1):85-101. doi: 10.1007/s00441-011-1199-1. Epub 2011 Jun 21. Review.
- Noncanonical TGF- $\beta$  signaling during mammary tumorigenesis. Parvani JG, Taylor MA, Schiemann WP.
- J Mammary Gland Biol Neoplasia. 2011 Jun;16(2):127-46. doi: 10.1007/s10911-011-9207-3. Epub 2011 Mar 31. Review.
- Beta3 integrin and Src facilitate transforming growth factor-beta mediated induction of epithelial-mesenchymal transition in mammary epithelial cells.
- Galliher AJ, Schiemann WP. Breast Cancer Res. 2006;8(4):R42.
- TGF- $\beta$  signaling and epithelial-mesenchymal transition in cancer progression. Katsuno Y, Lamouille S, Derynck R. Curr Opin Oncol. 2013 Jan;25(1):76-84. doi: 10.1097/CCO.0b013e32835b6371. Review.



- Transforming growth factor-beta signaling in epithelial-mesenchymal transition and progression of cancer. Miyazono K. Proc Jpn Acad Ser B Phys Biol Sci. 2009;85(8):314-23. Review.
- TGF-beta1 causes epithelial-mesenchymal transition in HaCaT derivatives, but induces expression of COX-2 and migration only in benign, not in malignant keratinocytes.
- Räsänen K, Vaheri A. J Dermatol Sci. 2010 May;58(2):97-104. doi: 10.1016/j.jdermsci.2010.03.002. Epub 2010 Mar 17.
- The relevance of the TGF- $\beta$  Paradox to EMT-MET programs. Morrison CD, Parvani JG, Schiemann WP. Cancer Lett. 2013 Nov 28;341(1):30-40. doi: 10.1016/j.canlet.2013.02.048. Epub 2013 Mar 5. Review.
- Distinct mechanisms of TGF-beta1-mediated epithelial-to-mesenchymal transition and metastasis during skin carcinogenesis.
- Han G, Lu SL, Li AG, He W, Corless CL, Kulesz-Martin M, Wang XJ. J Clin Invest. 2005 Jul;115(7):1714-23. Epub 2005 Jun 2.
- Synergistic effects of particulate matter and substrate stiffness on epithelial-to-mesenchymal transition. Barker TH, Dysart MM, Brown AC, Douglas AM, Fiore VF, Russell AG; HEI Health Review Committee. Res Rep Health Eff Inst. 2014 Nov;(182):3-41.

- mTOR
- 
- Cell size and invasion in TGF-beta-induced epithelial to mesenchymal transition is regulated by activation of the mTOR pathway.  
Lamouille S, Derynck R.  
J Cell Biol. 2007 Jul 30;178(3):437-51. Epub 2007 Jul 23.
- Transforming Growth Factor  $\beta$ 1-induced Apoptosis in Podocytes via the Extracellular Signal-regulated Kinase- Mammalian Target of Rapamycin Complex 1-NADPH Oxidase 4 Axis.  
Das R, Xu S, Nguyen TT, Quan X, Choi SK, Kim SJ, Lee EY, Cha SK, Park KS.  
J Biol Chem. 2015 Dec 25;290(52):30830-42. doi: 10.1074/jbc.M115.703116. Epub 2015 Nov 12.
- Mammalian Target of Rapamycin (mTOR) Regulates Transforming Growth Factor- $\beta$ 1 (TGF- $\beta$ 1)-Induced Epithelial- Mesenchymal Transition via Decreased Pyruvate Kinase M2 (PKM2) Expression in Cervical Cancer Cells.  
Cheng KY, Hao M.  
Med Sci Monit. 2017 Apr 27;23:2017-2028.
- TGF- $\beta$ -induced activation of mTOR complex 2 drives epithelial-mesenchymal transition and cell invasion. Lamouille S, Connolly E, Smyth JW, Akhurst RJ, Derynck R.  
J Cell Sci. 2012 Mar 1;125(Pt 5):1259-73. doi: 10.1242/jcs.095299. Epub 2012 Mar 7.
- Metformin Inhibits TGF- $\beta$ 1-Induced Epithelial-to-Mesenchymal Transition via PKM2 Relative-mTOR/p70s6k Signaling Pathway in Cervical Carcinoma Cells.  
Cheng K, Hao M.  
Int J Mol Sci. 2016 Nov 30;17(12). pii: E2000.