Historically

- From 80's to early 2000's, Biophysicists interests in

Endothelial cell structural reactions to blood hydrodynamics stress Ex: Martin Schwartz Cytoskeleton reorganisation, cell division control

<u>Tumour cell</u> structural <u>reactions to fibrotic stiffness:</u> Ex: Mina Bissel, Valérie Weaver (UCSF), Cell culture, cytoskeleton reorganisation,cell division control

- From early 2000's to now, Biophysicists interests in

Cell differentiation in response to strain in vivo (E. Farge (I. Curie, 2003 to now) *and to stifness in cell culture* (D. Disher, U-Penn, 2006 to now)





Mechanotransductive Activation of \beta-catenin:

from Mesoderm Evolutionary Emergence to Cancer Progression

I- Evolutionary implication in mechanotransduction in mesoderm origins, 600 millions years ago

II- From development to cancer: tumour growth mechanical cues in the reactivation of mechanosensitive embryonic pathways





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Introduction: mechanotransductive cues in embryonic development regulation



Length, 500 microns

6000 cells surrounding a yolk

Costa et al, Development 1993

Supatto et al, PNAS, 2005



Background - Embryogenesis: Patterning and Mechanical Morphogenesis





1- Mechanical Induction of Twist Expression in Presumive Anterior Mid-**Gut Cells**



Is Twist Mechano-sensitivity Involved during Endogenous Embryonic Morphogenesis?





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Rescuing Stomodeal Compression with Physiologically Relevant Dynamics and Forces by using a <u>Magnetic Tweezers in Photo-Ablated Embryos</u>





Mechanical Rescue of Twist Stomodeal Expression in the Wild Type, with Physiologically Relevant Compression Strain



I = 18% + 10% (n=42) I = 79% + 10% (n=32)

Nicolas Desprat et al, Dev Cell 2008

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Physiological Function for Twist in Anterior Gut Track Formation?





Atlas from Hartenstein et al 1985

Physiological Function: middle mid-gut Dve differentiation



I= 34% +- 6% (83%, n=22)

78%, n=36 (Larvae Lethal, at 3rd Stage)

Nicolas Desprat et al, Dev Cell 2008



Mechano-Transduction Pathway: β-catenin/Armadillo is involved in the Mechano-Transcriptional Pathway



β-catenin/Armadillo is also involved as a Mechano-Transcriptional Pathway in Bone Development

JOURNAL OF BONE AND MINERAL RESEARCH Volume 20, Number 7, 2005 Published online on February 14, 2005; doi: 10.1359/JBMR.050210 © 2005 American Society for Bone and Mineral Research

TOPGAL Mice Show That the Canonical Wnt Signaling Pathway Is Active During Bone Development and Growth and Is Activated by Mechanical Loading In Vitro

Julie R Hens,1 Kimberly M Wilson,2 Pamela Dann,1 Xuesong Chen,1 Mark C Horowitz,2 and John J Wysolmerski1



Hens et al, Journal of Bone and Mineral Research, 2005

Muscle Contraction Is Necessary to Maintain Joint Progenitor Cell Fate

Joy Kahn,^{1,6} Yulia Shwartz,^{1,6} Einat Biltz,¹ Sharon Krief,¹ Amnon Sharir,^{1,2} Dario. A. Breitel,¹ Pevital Rattenbach,³ Frederic Relax,³ Pascal Maire,⁴ Ryan B. Rourtnee,⁶ David M. Kingsley,⁶ and Elazar Zeizer^{1,6} ¹Department of Molecular Genetics, Weizmann Institute of Science, Rehovt 76100, Israel ²The Laboratory of Musculcekeletal Biomechanics and Applied Anatomy, Koret School of Veterinary Medicine, Hebrew University of Jeusalem, Rehovet 76100, Israel ³MUD 6.726 Musculcekeeletal Biomechanics (Science, Rehovet School of Veterinary Medicine, Hebrew University of Jeusalem, Rehovet 76100, Israel ³MUD 6.726 Musculcekeeletal Biomechanics (Science, Rehovet School of Veterinary Medicine, ³MUD 6.726 Musculcekeeletal Biomechanics (Science, Rehovet School of Veterinary Medicine, ³MUD 6.726 Musculcekeeletal Biomechanics (Science, Rehovet School of Veterinary Medicine, ³MUD 6.726 Musculcekeeletal Biomechanics (Science, Rehovet School of Veterinary Medicine, ³MUD 6.726 Musculcekeeletal Biomechanics (Science, Rehovet 76100, Israel

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Figure 1. Joint Loss in the Absence of Muscle Contraction

Bone Development: Khan J et al, Dev Cell 2009

Inhibition of Adipogenesis

Sen, B, et al Endicronology, 2008



2- Mechanical activation of mesoderm invagination

Myo-II Apical Stabilisation generates Mesoderm Invagination



D. Kiehart, M. Leptin, E. Wieschaus, N. Perrimon groups et al. 13 - 11/10/15



There exists two phases of apical constriction: is the second mechanically triggered by the first?



M. Leptin, E. Wieschaus, N. Perrimon et al. Groups

Sweeton et al, Development, 1991 A. Martin et al, Nature 2009



Indenting sna mutants to rescue the missing mechanical strains of the first constricting stochastic phase, rescues the second coordinated constriction phase and mesoderm invagination



Pouille, Ahmadi et al, Science Signalling, 2009 Demosthène Mitrossilis et al., submitted



-> Mechanical Indentation Rescues Myo-II Apical Redistribution and Mesoderm Invagination in *sna-/sna-*



Pouille, Ahmadi et al, Science Signalling, 2009

Stats: - 14/15 in indented early-stage 6 (67% full, 26% partial) - 9/14 in globally deformed



I- Evolutionary implication of mechanotransductive β -cat activation in mesoderm emergence, 600 millions years ago

Second mechanotransductive wave: β -catenin phosphorylation of Y667, impairing β -catenin interaction with E-cadherin, is mechanically induced by mesoderm

invagination





β-catenin cytoplasmic and nuclear translocation are mechanically induced by Y667 β -catenin mechanical phosphorylation and lead to Twist expression maintenance in the mesoderm



Note: 1% FA Fix procedure for Arm nuclei detection (poor junctional resolution)



Zebrafish: the mesoderm patterning gene *notail* is expressed at the onset of epiboly in specifically deformed margin cells in a β-catenin dependent but Wnt independent process





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The β -catenin dependent expression of *notail* in margin cells is induced by the morphogenetic movement of epiboly onset



Uniaxial deformation: 35µm during 20min



-> Magnetic rescue of epiboly initiation *in vivo*



Endogenous: 0.22 +- 0.04 μm/min 21 - - 11/10/15 Bleb: not detectable Magnetic: 0.25 +- 0.06 μm/min (Poky: fluctuations of 1 μm/min) institutCurie

Nuclear translocation of β -catenin and *notail* expression are triggered by mechanical induction of phosphorylation of the Y667- β -catenin at the onset of epiboly





Conclusion I

Mechanical induction of the β -cat/mesoderm pathway at the origin of mesoderm emergence leading to the Diploblast-Tribloblast evolutionary transition ?



T. Brunet, Adrien Bouclet et al, Nature Communications, 2013



FONDATION RECHERCHE MÉDICALE Mechanics & Genetics of **Embryonic and Tumour Development**

-Joanne Whitehead, Sandrine Barbier and Elena Fernandez-Sanchez -Tumoral Progression / Post-docs IC-Marie Curie, ANR, RTRA FPGDG

-Ferromagnetic Injections and Mechano-transcription Post-doc INSERM







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-T. Brunet, Adrien Bouclet, L. Henry, F. Serman

Benjamin Driquez, Willy Supatto, A. Bouclet -Numerical simulations and experiments -PhD 2005/2009, Microsoft European Grant

-Collaborators:

-Nicolas Desprat

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