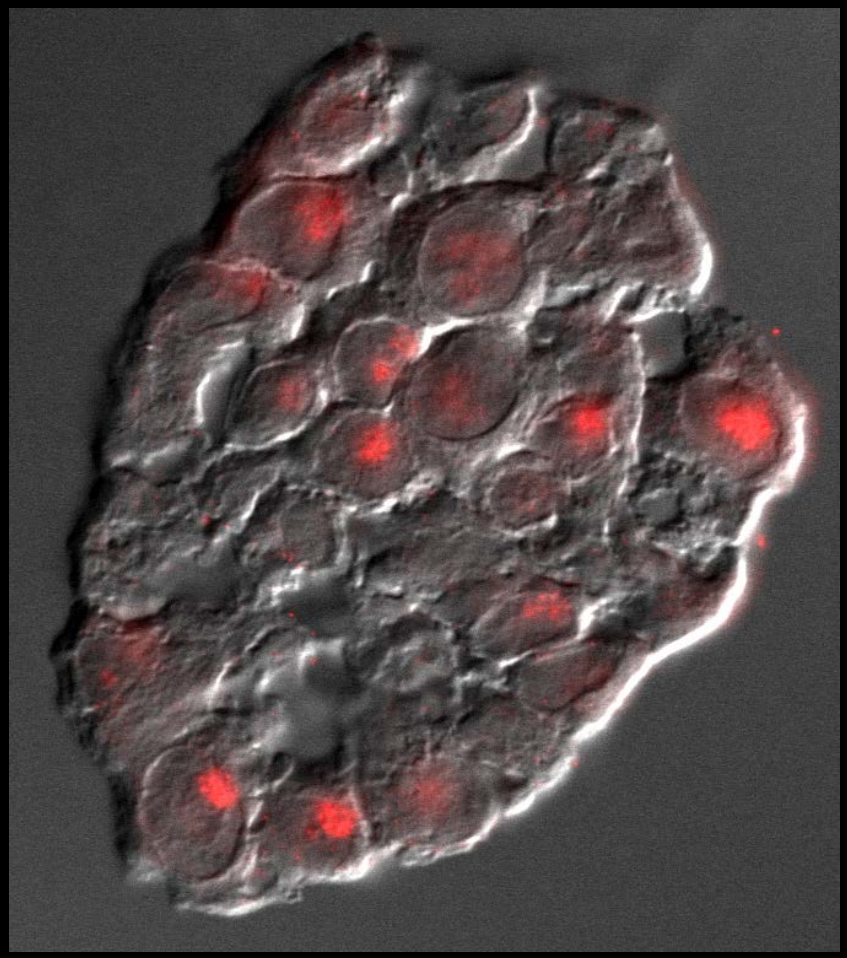
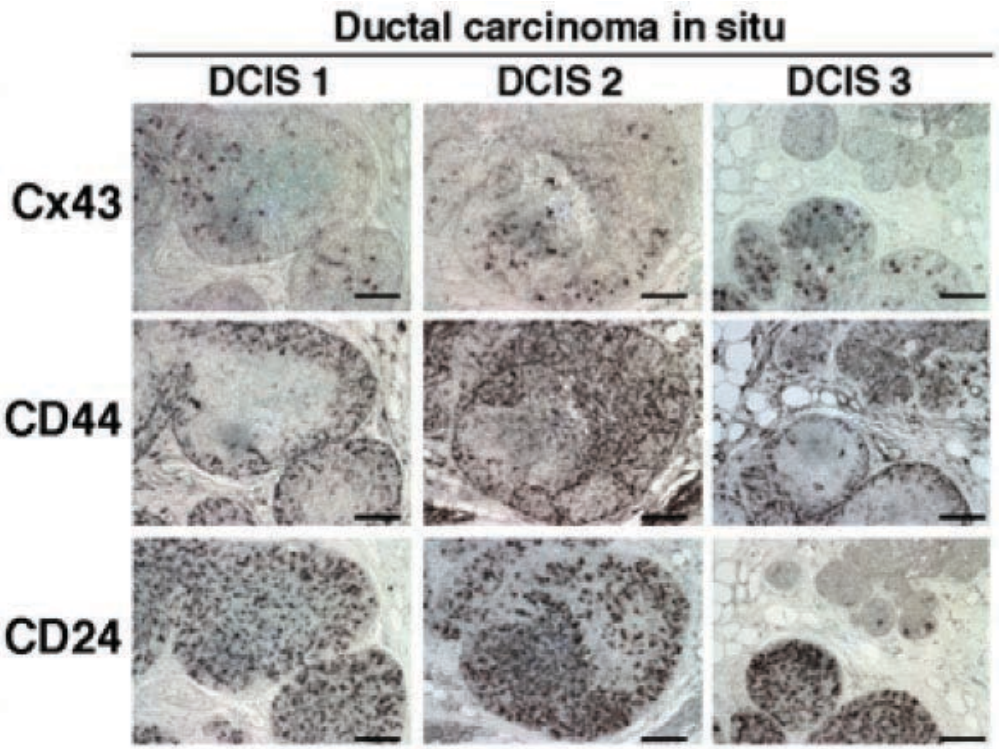


TGFBR3

Applications of stochastic profling

Kevin Janes
Department of Biomedical Engineering
University of Virginia

The breast-cancer mosaic

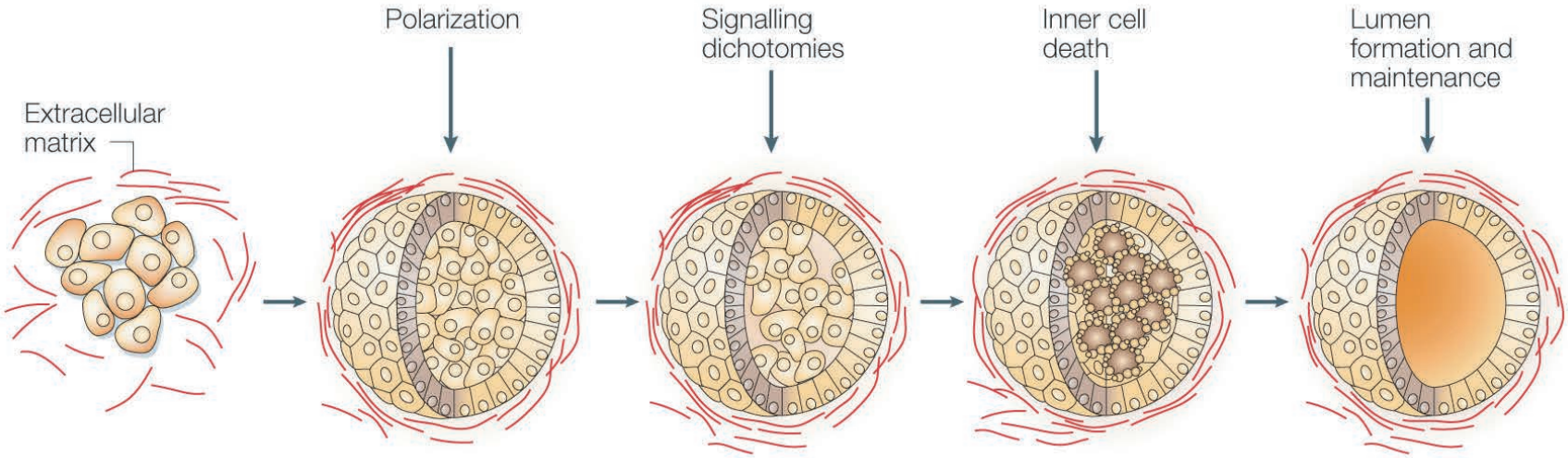


Shipitsin et al., *Cancer Cell* **11**:259 (2007)

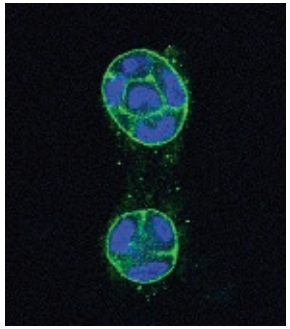
Antonio Gaudi, Parc Güell

What role does intratumor heterogeneity play in cancer progression?

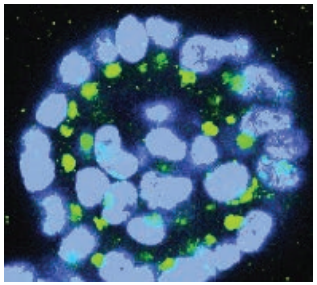
Heterogeneities during in vitro mammary acinar morphogenesis



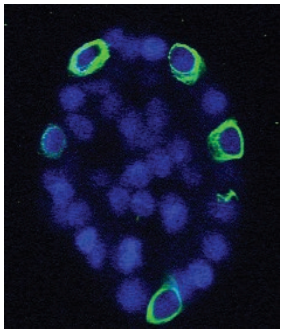
Laminin 5



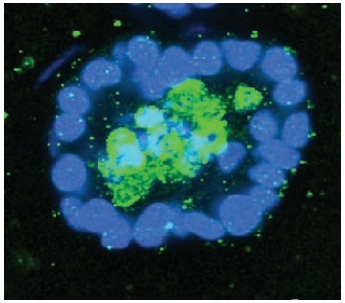
GM130 (Golgi)



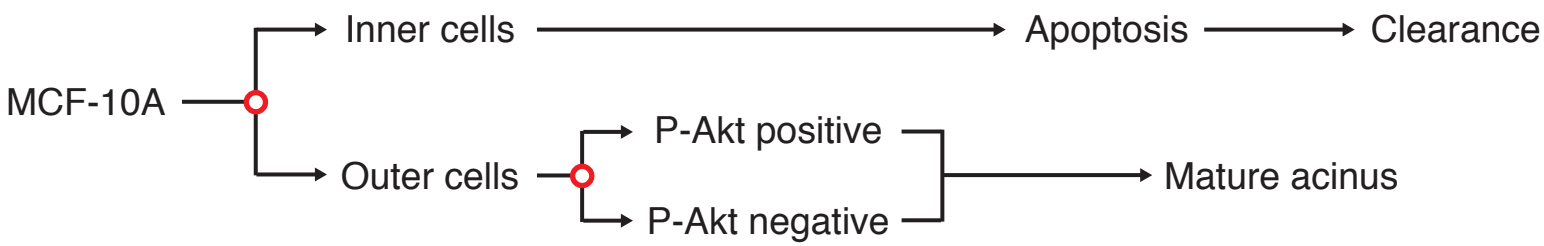
phospho-Akt



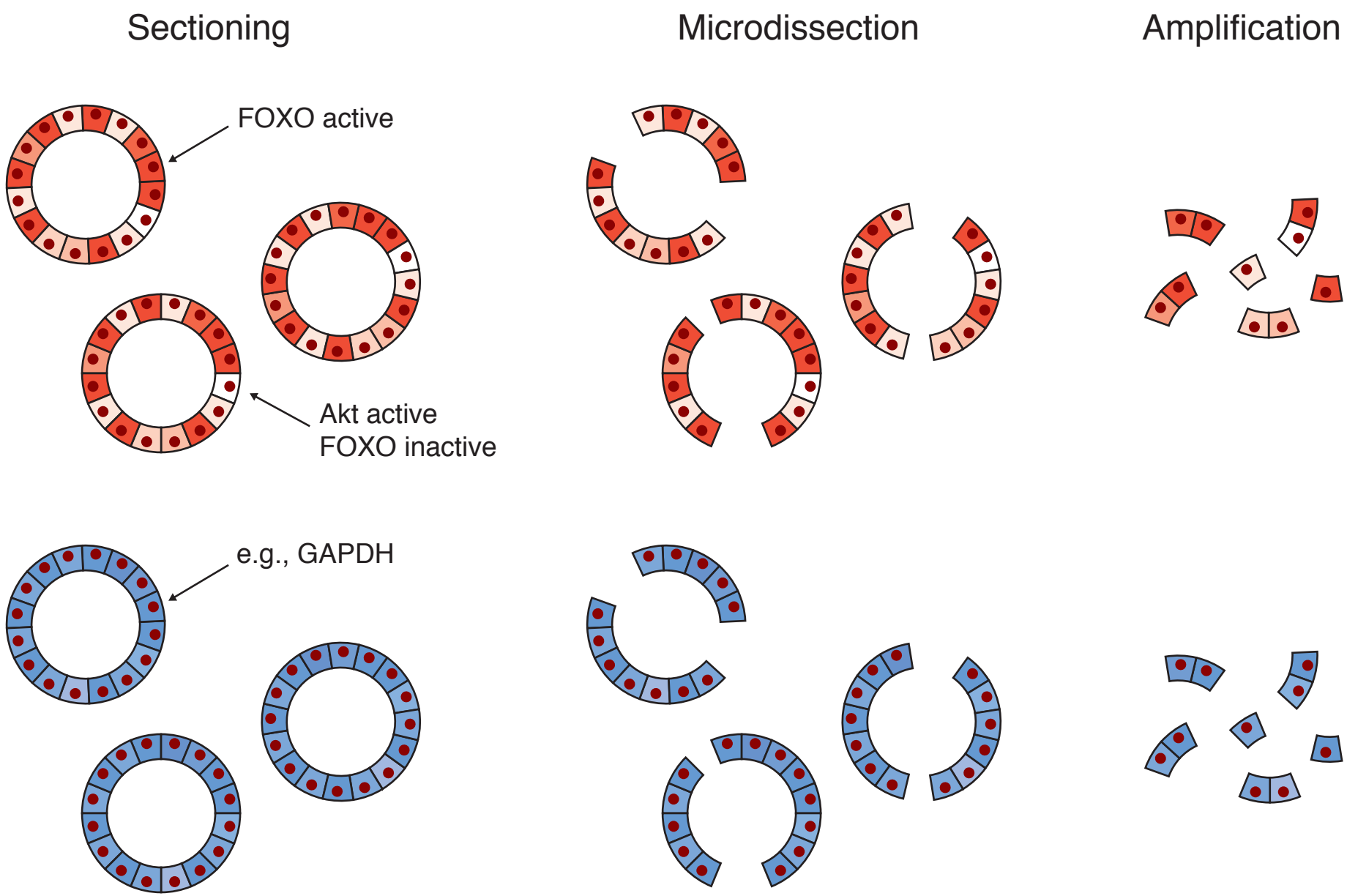
cleaved caspase-3



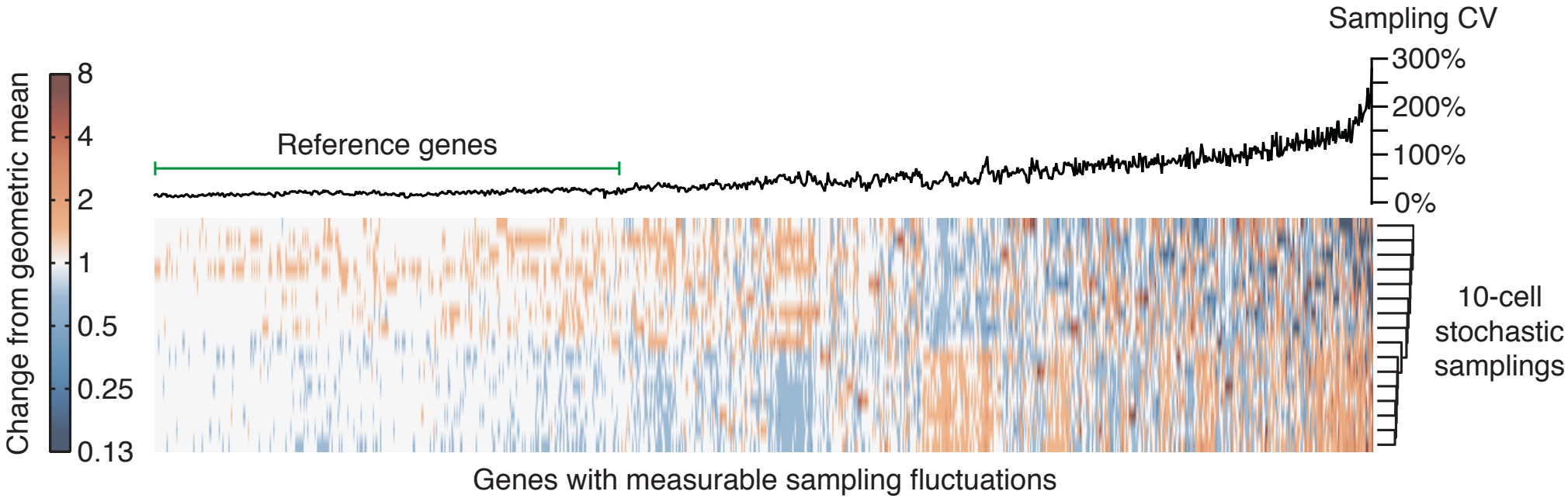
Debnath and Brugge, Nat. Rev. Cancer (2005)



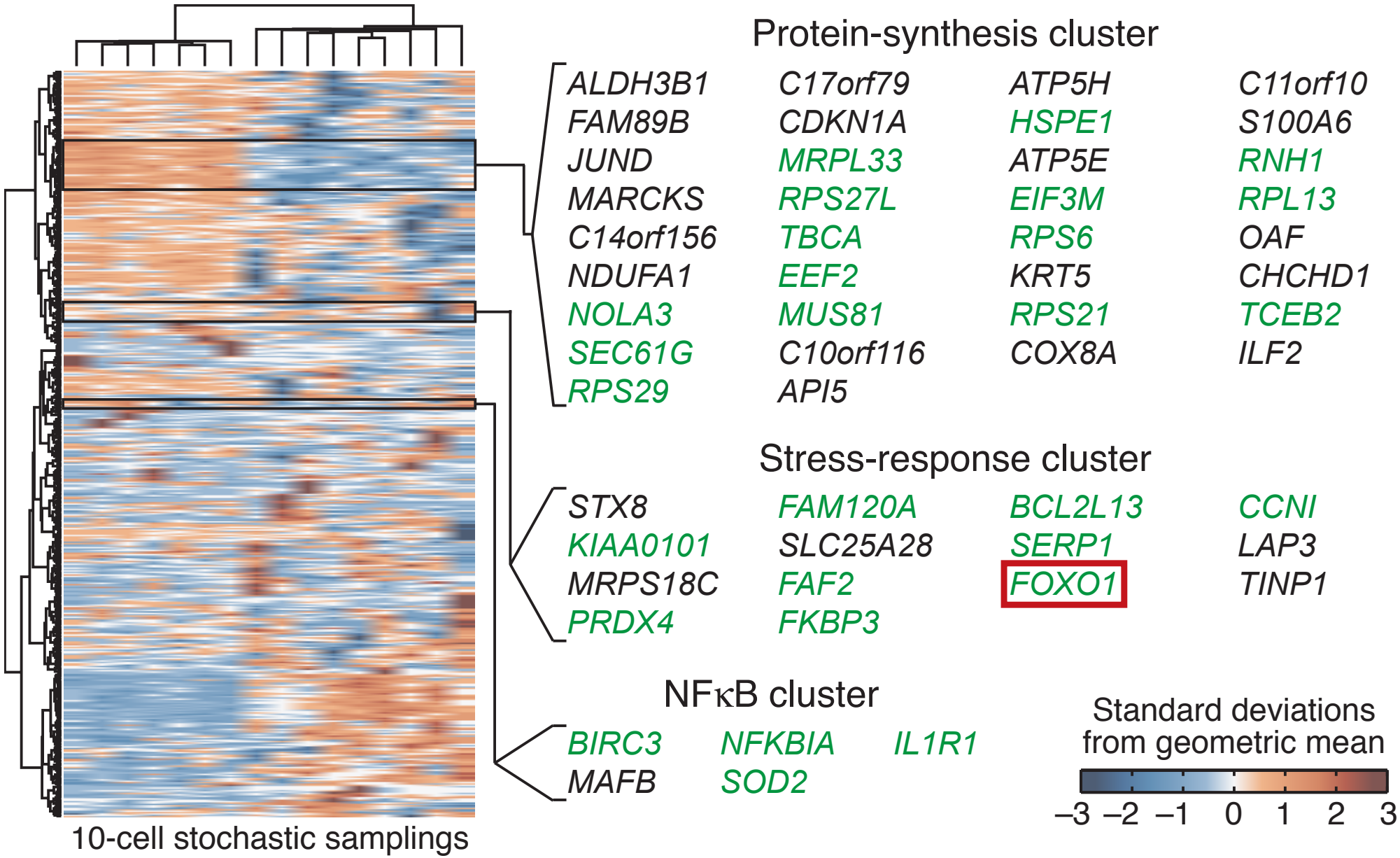
Identifying heterogeneously expressed FOXO targets



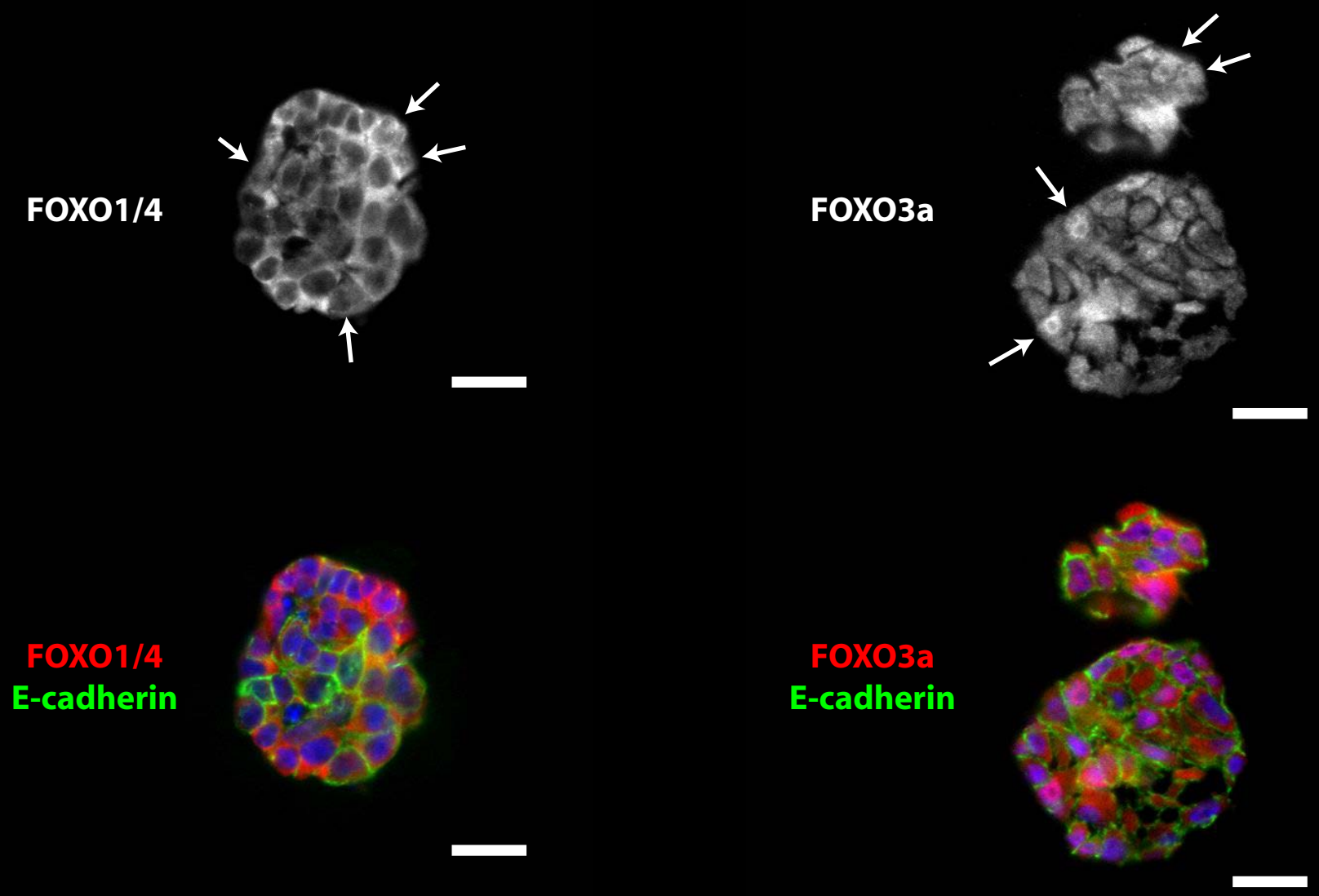
Stochastic profling of single-cell heterogeneities in matrix-attached cells



Single-cell coregulatory programs identified by stochastic sampling

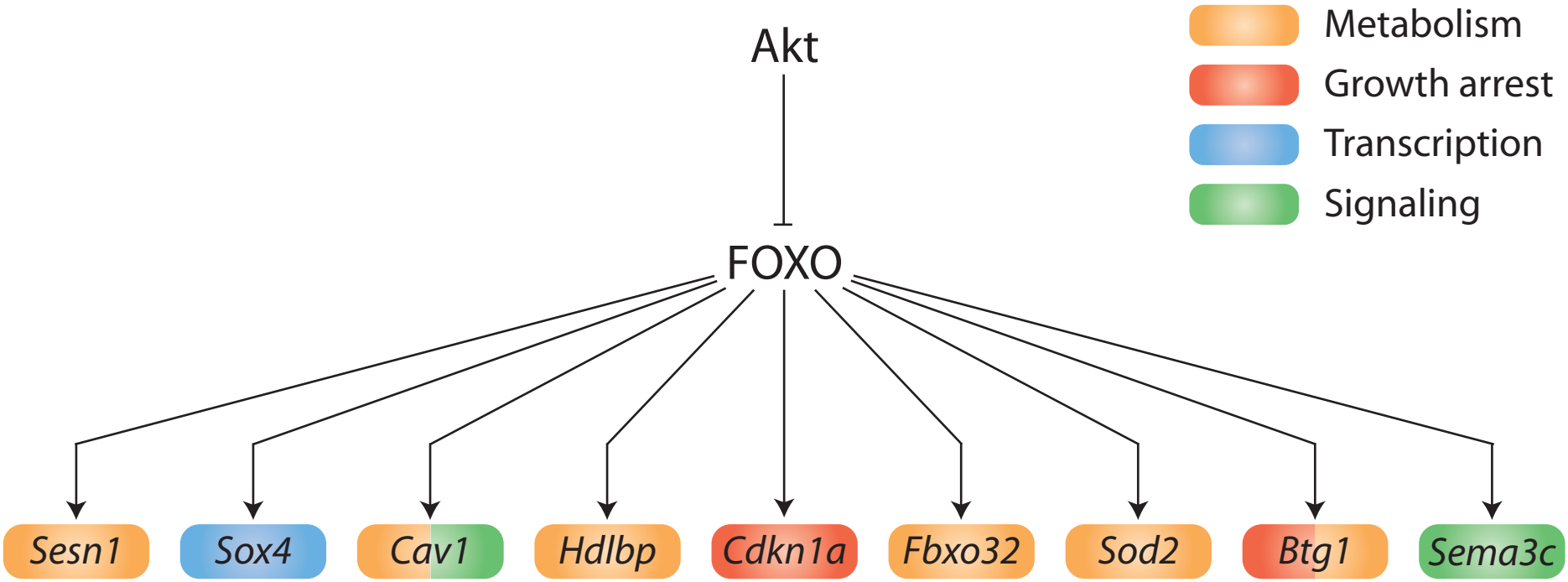


Dichotomous nucleocytoplasmic localization of FOXO-family members

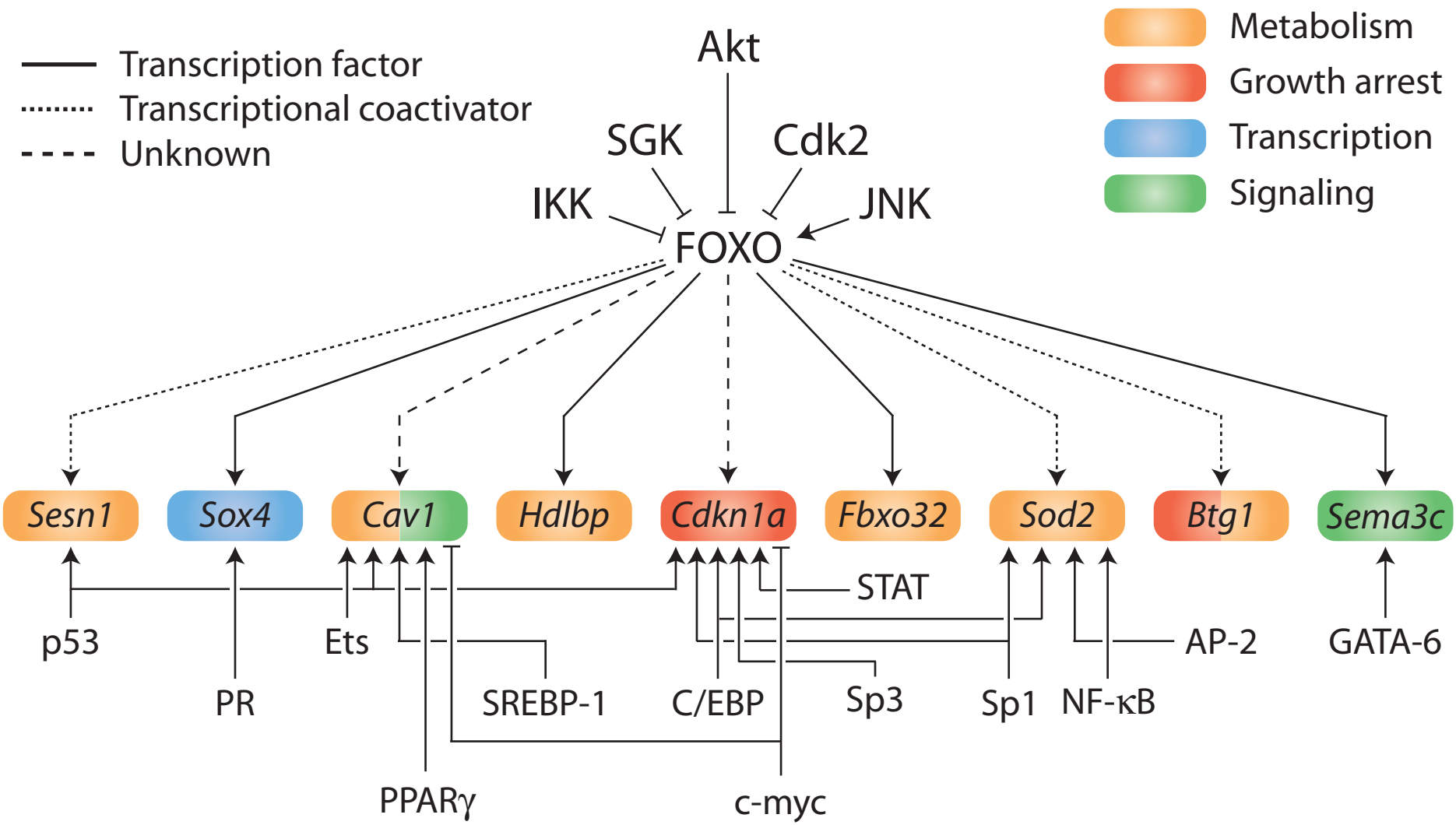


MCF10A-5E, day 10
Scale bar: 25 μm

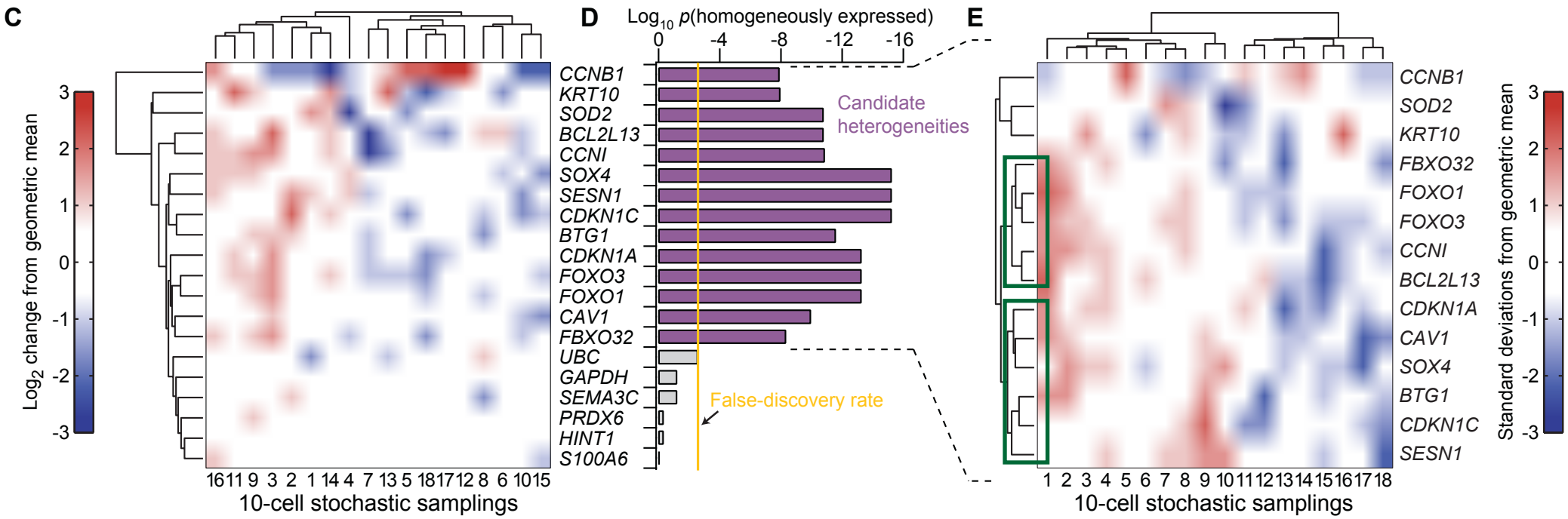
The FOXO regulatory network



The FOXO regulatory network

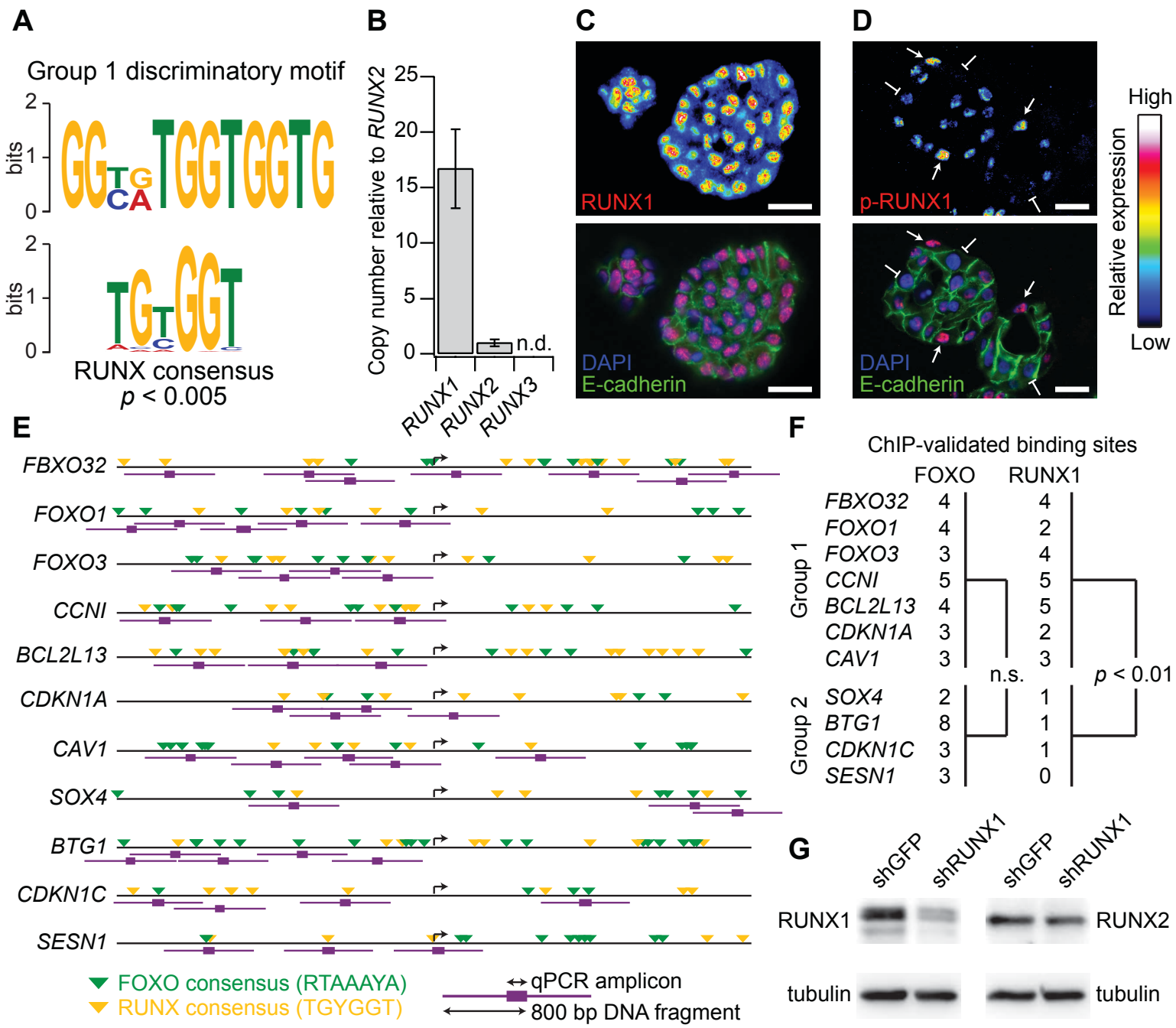


Stochastic profiling identifies two groups of FOXO-regulated genes



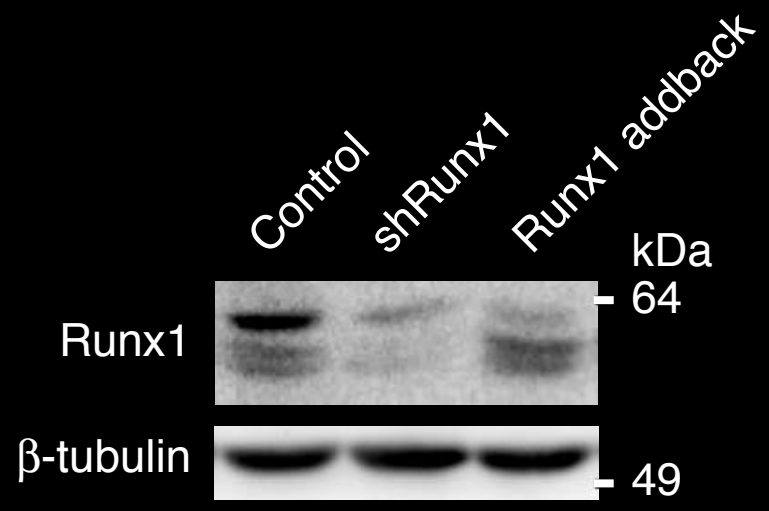
Wang et al., *Proc Natl Acad Sci* **108**:E803-12 (2011)

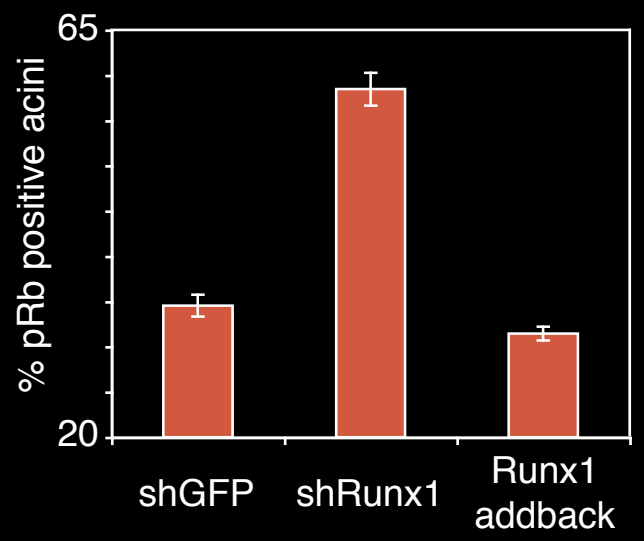
Stochastic profiling combined with bioinformatics identifies transcription coregulation between FOXOs and Runx1

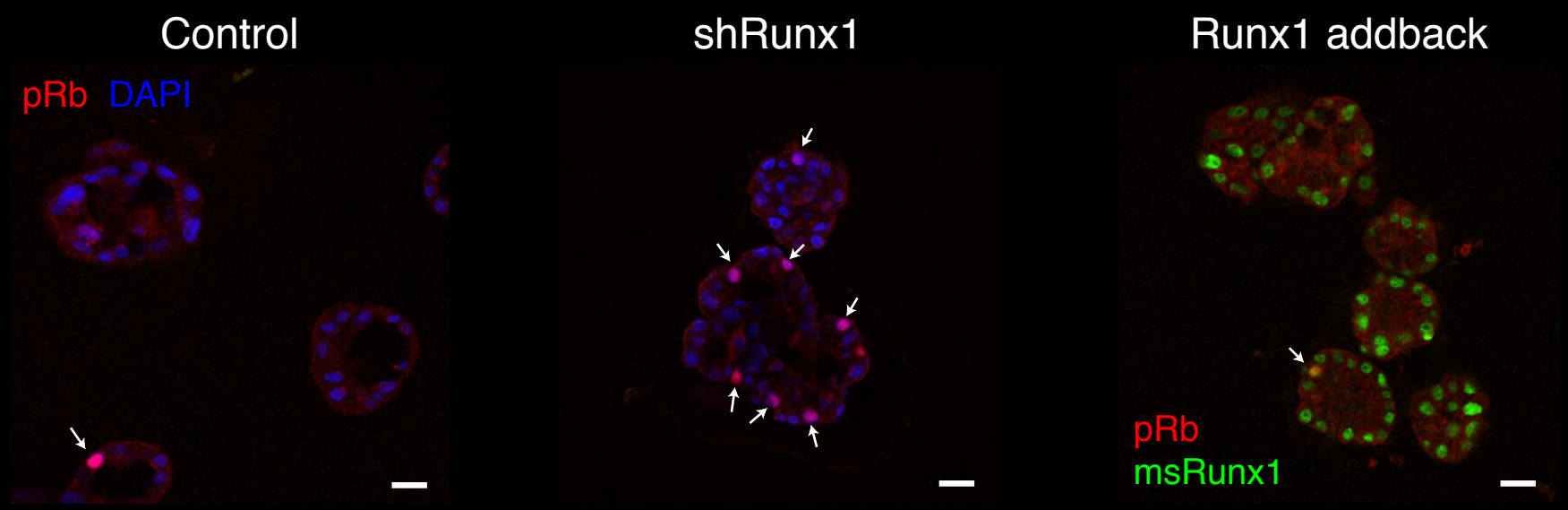


Wang et al., *Proc Natl Acad Sci* **108**:E803-12 (2011)

Delayed growth arrest and altered acinar morphology in Runx1 knockdown structures

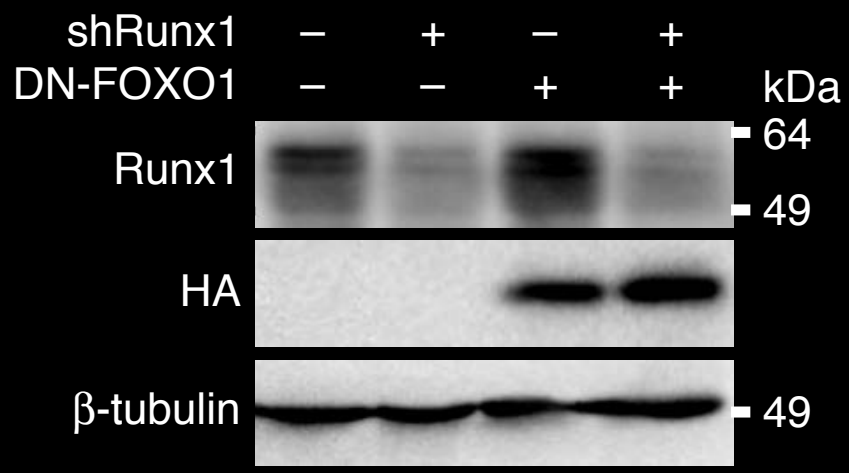


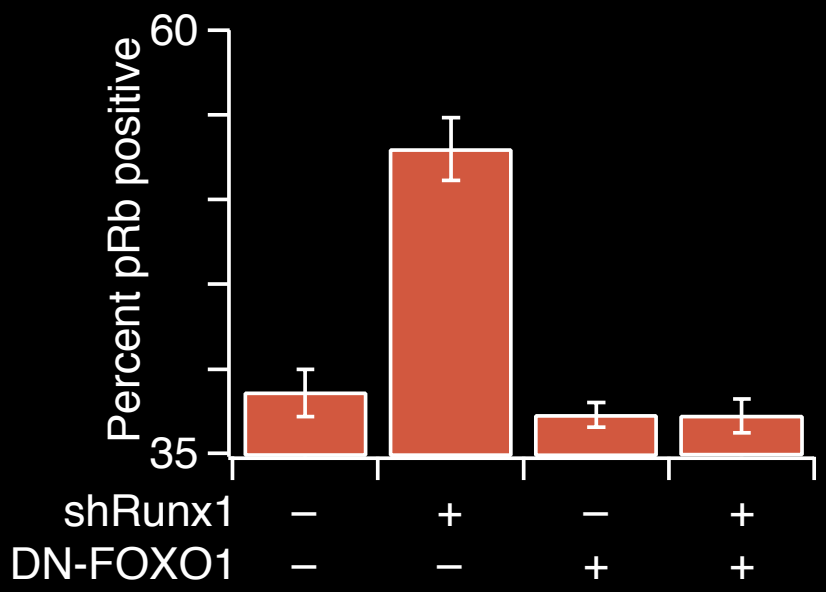


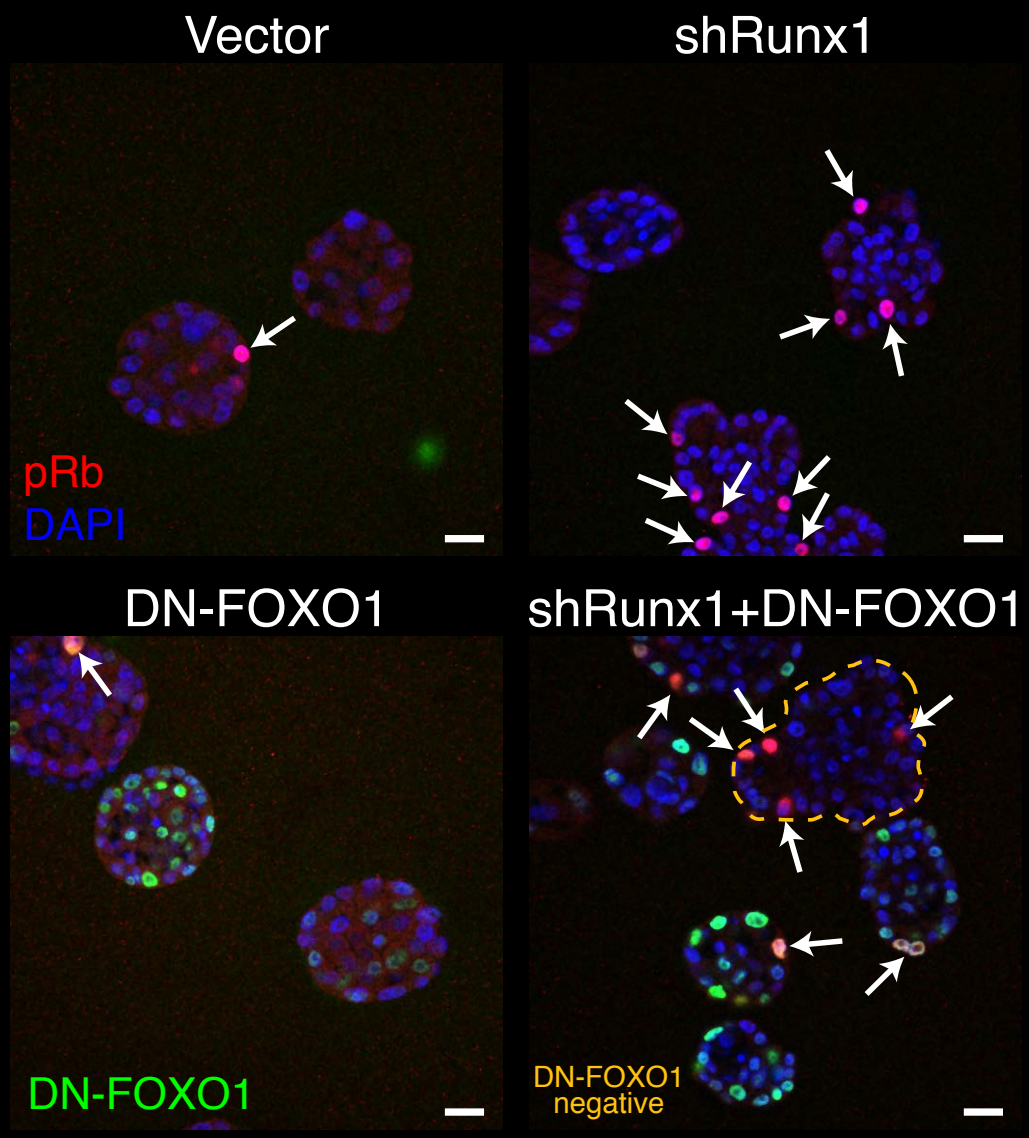


MCF10-5E, day 14
Scale bar: 25 μm

shRunx1 phenotypes are blocked by homogenization of FOXO signaling

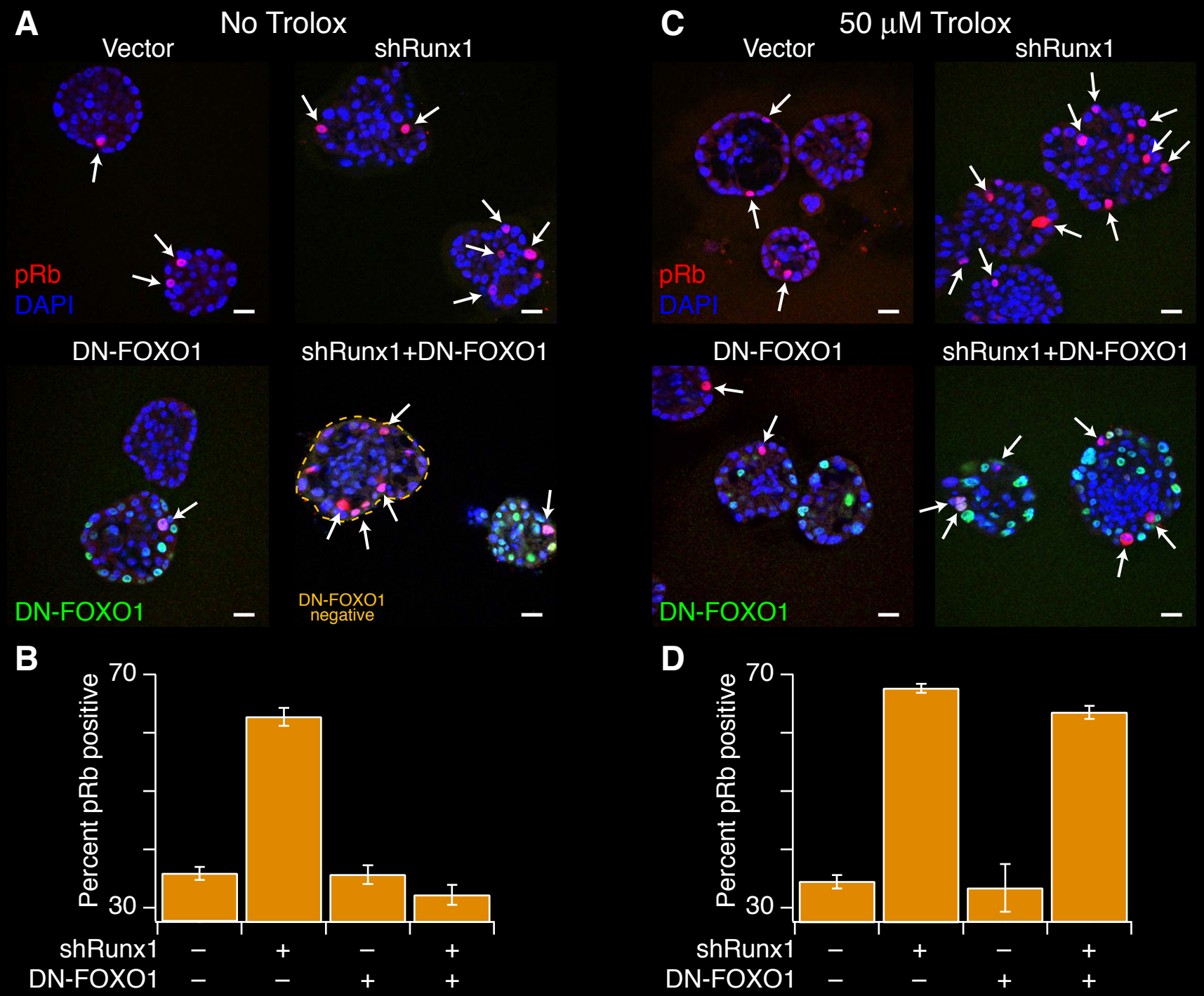






MCF10-5E, day 14
Scale bar: 25 μm

FOXO-Runx1 crosstalk is blocked by anti-oxidants



EXTRA VIEW

Cell Cycle 10:20, 3461-3465; October 15, 2011; © 2011 Landes Bioscience

RUNX1 and its understudied role in breast cancer

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ARTICLE

doi:10.1038/nature11143

Whole-genome analysis informs breast cancer response to aromatase inhibition

Matthew J. Ellis[1,2,3]*, Li Ding[4,5]*, Dong Shen[4,5]*, Jingqin Luo[3,6], Vera J. Suman[7], John W. Wallis[4,5], Brian A. Van Tine[1], Jeremy Hoog[1], Reece J. Goiffon[8,9,10], Theodore C. Goldstein[11], Sam Ng[11], Li Lin[1], Robert Crowder[1], Jacqueline Snider[1], Karla Ballman[7], Jason Weber[1,8,12], Ken Chen[13], Daniel C. Koboldt[4,5], Cyriac Kandoth[4,5], William S. Schierding[4,5], Joshua F. McMichael[4,5], Christopher A. Miller[4,5], Charles Lu[4,5], Christopher C. Harris[4,5], Michael D. McLellan[4,5], Michael C. Wendl[4,5], Katherine DeSchryver[1], D. Craig Allred[3,14], Laura Esserman[15], Gary Unzeitig[16], Julie Margenthaler[2], G. V. Babiera[13], P. Kelly Marcom[17], J. M. Guenther[18], Marilyn Leitch[19], Kelly Hunt[13], John Olson[17], Yu Tao[6], Christopher A. Maher[1,4], Lucinda L. Fulton[4,5], Robert S. Fulton[4,5], Michelle Harrison[4,5], Ben Oberkfell[4,5], Feiyu Du[4,5], Ryan Demeter[4,5], Tammi L. Vickery[4,5], Adnan Elhammali[8,9,10], Helen Piwnica-Worms[8,12,20,21], Sandra McDonald[2,22], Mark Watson[6,14,22], David J. Dooling[4,5], David Ota[23], Li-Wei Chang[3,14], Ron Bose[2,3], Timothy J. Ley[1,2,4], David Piwnica-Worms[8,9,10,12,24], Joshua M. Stuart[11], Richard K. Wilson[2,4,5] & Elaine R. Mardis[2,4,5]

LETTER

doi:10.1038/nature11154

Sequence analysis of mutations and translocations across breast cancer subtypes

Shantanu Banerji[1,2,3]†*, Kristian Cibulskis[1]*, Claudia Rangel-Escareno[4]*, Kristin K. Brown[5]*, Scott L. Carter[1], Abbie M. Frederick[1], Michael S. Lawrence[1], Andrey Y. Sivachenko[1], Carrie Sougnez[1], Lihua Zou[1], Maria L. Cortes[1], Juan C. Fernandez-Lopez[4], Shouyong Peng[2], Kristin G. Ardlie[1], Daniel Auclair[1], Veronica Bautista-Piña[6], Fujiko Duke[1], Joshua Francis[1], Joonil Jung[1], Antonio Maffuz-Aziz[6], Robert C. Onofrio[1], Melissa Parkin[1], Nam H. Pho[1], Valeria Quintanar-Jurado[4], Alex H. Ramos[1], Rosa Rebollar-Vega[4], Sergio Rodriguez-Cuevas[6], Sandra L. Romero-Cordoba[4], Steven E. Schumacher[1,2], Nicolas Stransky[1], Kristin M. Thompson[1], Laura Uribe-Figueroa[4], Jose Baselga[3,7], Rameen Beroukhim[1,2,3,8], Kornelia Polyak[2,3,9], Dennis C. Sgroi[3,10], Andrea L. Richardson[2,3,11], Gerardo Jimenez-Sanchez[4]†, Eric S. Lander[1,3,12], Stacey B. Gabriel[1], Levi A. Garraway[1,2,3], Todd R. Golub[1,3,13,14], Jorge Melendez-Zajgla[4], Alex Toker[3,5], Gad Getz[1], Alfredo Hidalgo-Miranda[4] & Matthew Meyerson[1,2,3,8]

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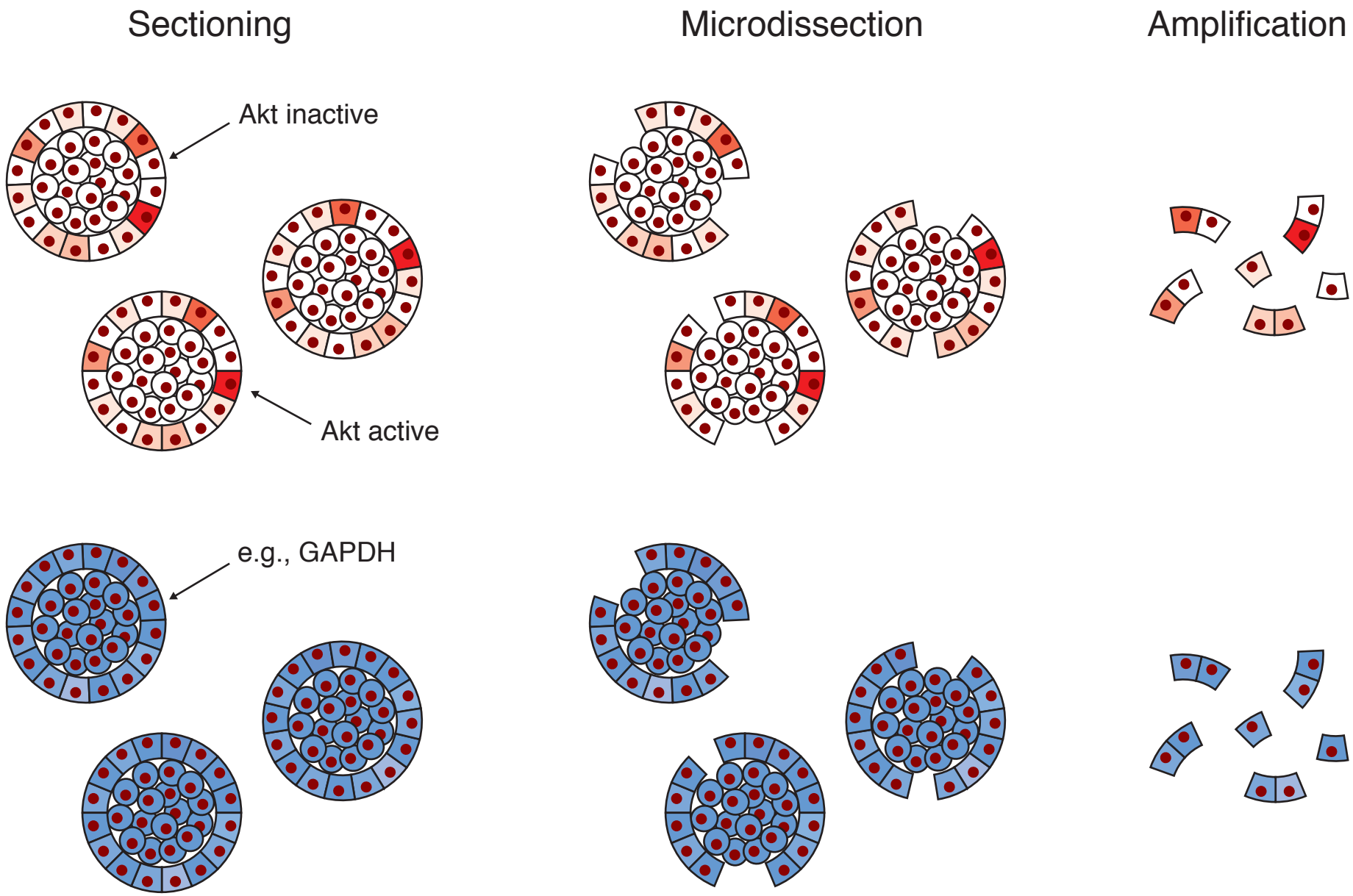
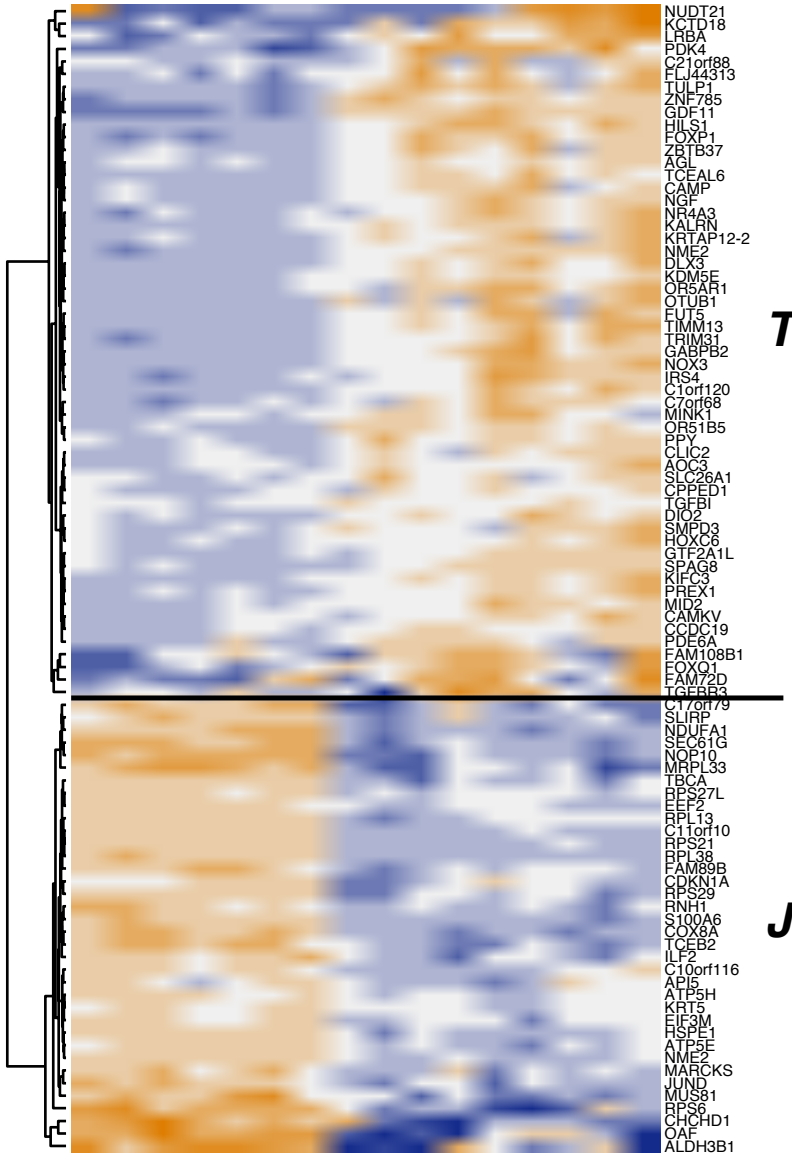
Identifying heterogeneously regulated expression programs among ECM-attached cells



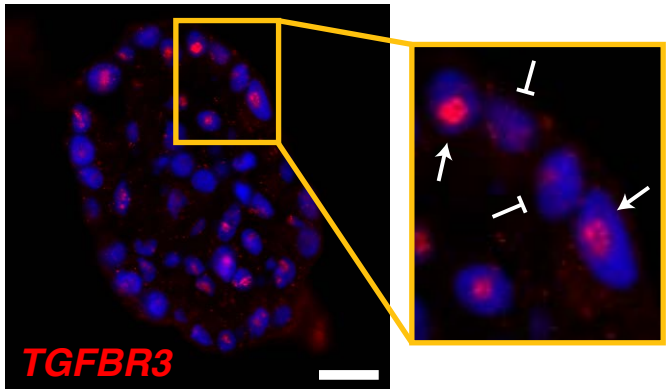
Janes et al., *Nat Methods* **7**:311-7 (2010)
Wang et al., *Proc Natl Acad Sci* **108**:E803-12 (2011)

A pair of anticorrelated expression programs identified by stochastic profiling

10-cell samplings of matrix-attached cells

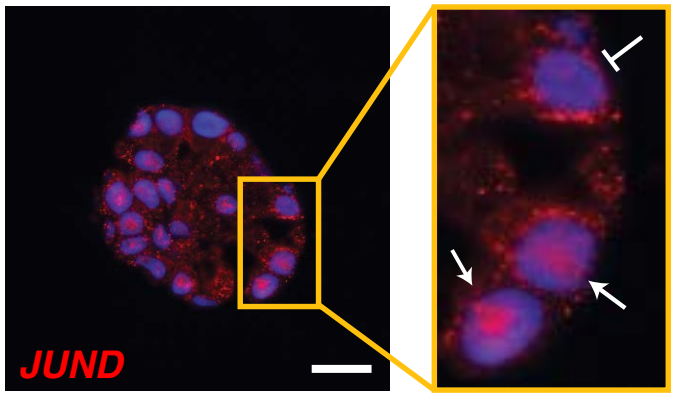


***TGFBR* cluster**



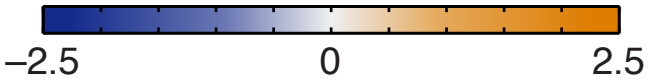
~30% *TGFBR3* positive

***JUND* cluster**



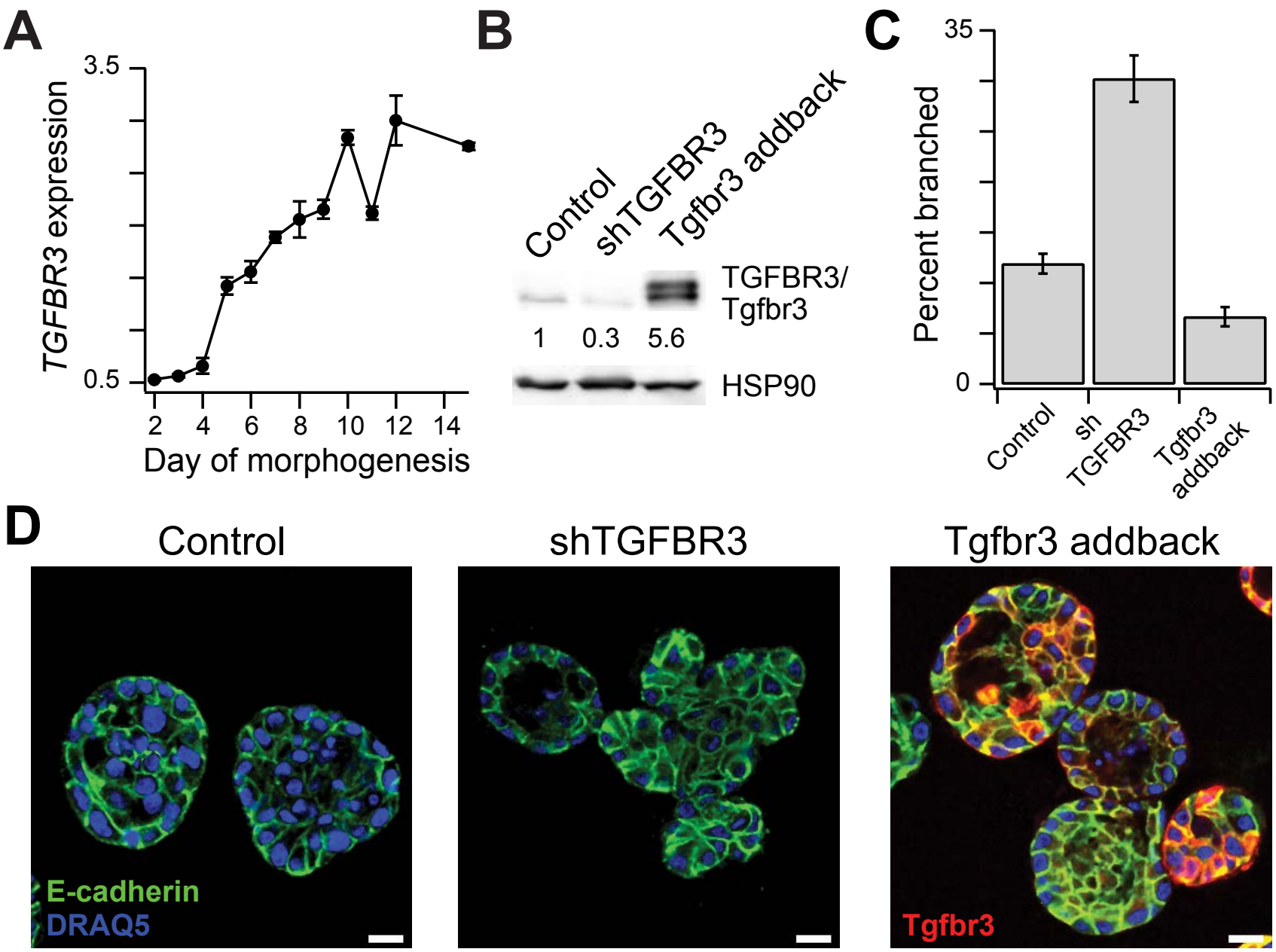
~75% *JUND* positive

Standard deviations from geometric mean



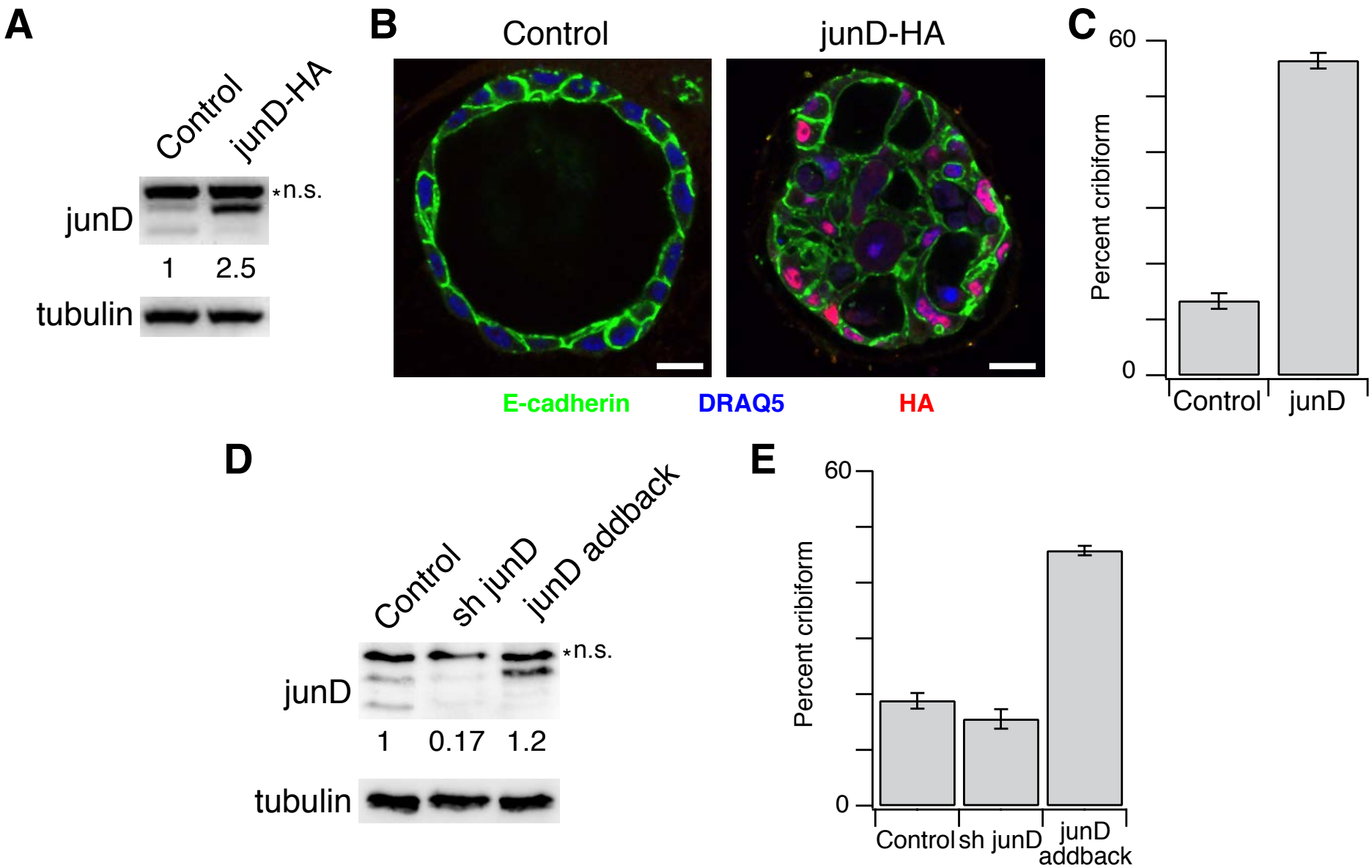
MCF10A-5E d10
Scale bar: 20 μm

TGFBR3 expression represses branch-like structures during morphogenesis

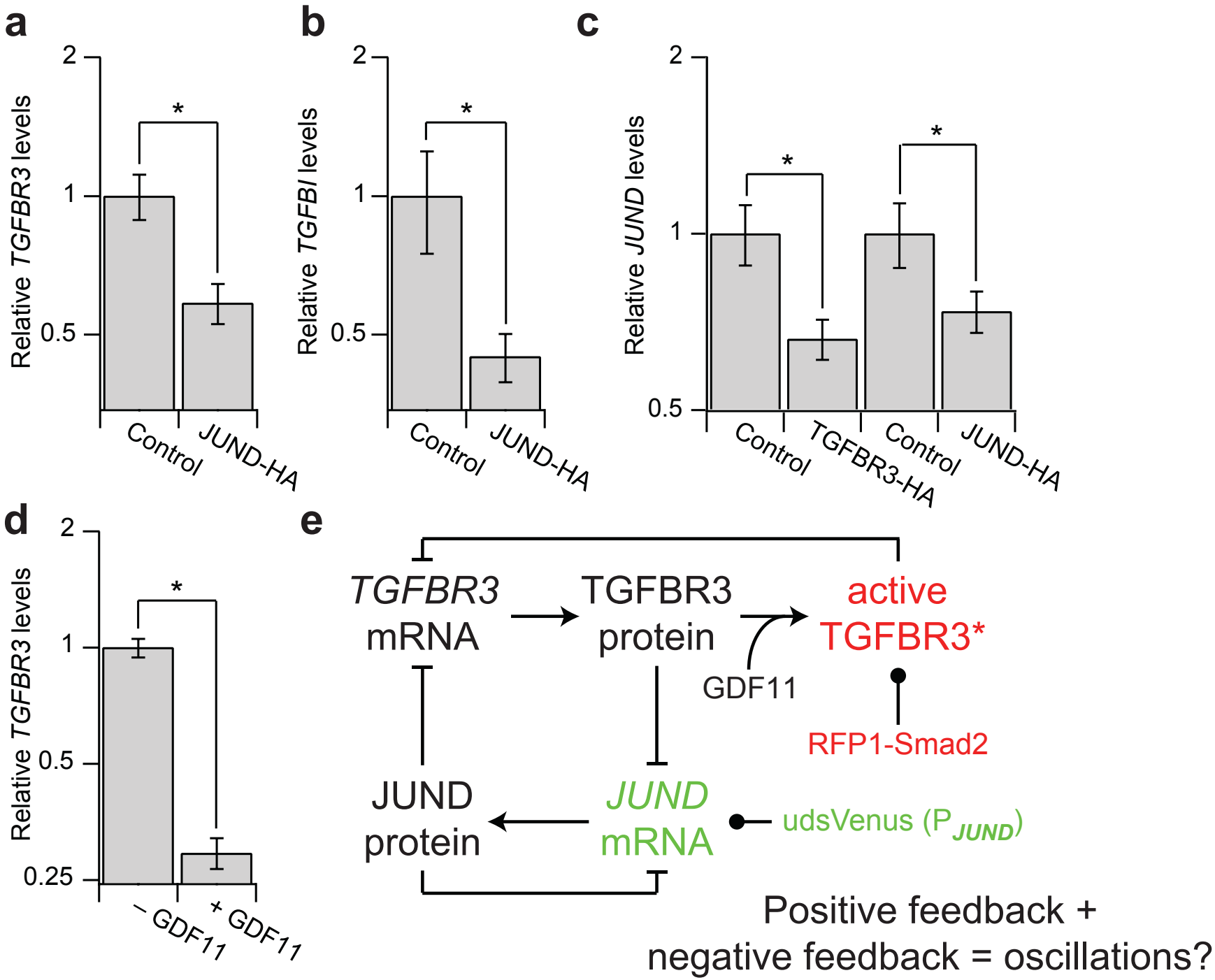


MCF10A-5E d10
Scale bar: 20 μm

Constitutive *JUND* expression causes stable cribiform-like structures during morphogenesis



An interlinked TGFBR3–JUND regulatory circuit in morphogenesis



The TGFBR3–JUND circuit gives rise to antiphase, damped oscillations