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Polarity reversal primes cell scattering during epithelial to mesenchymal transition

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HAL Authorization

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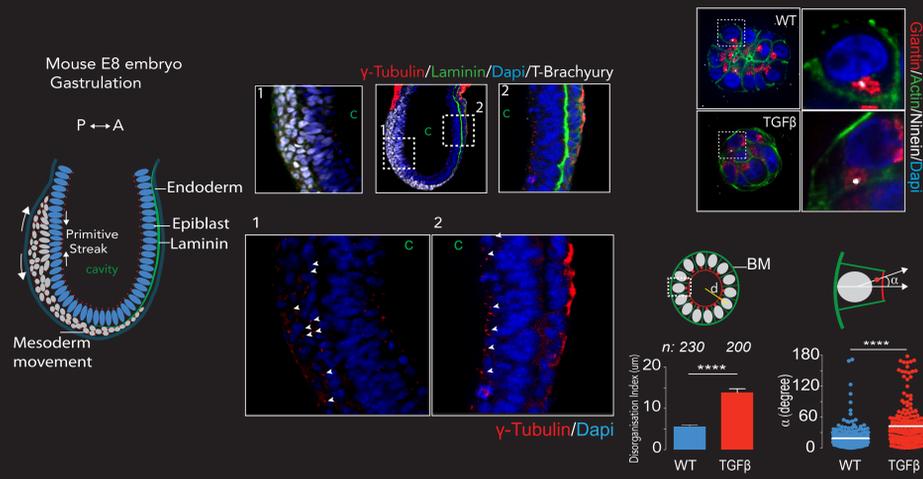
Abstract

Epithelial to mesenchymal transition (EMT) is a morphogenetic event that takes place during specific stages of embryo development and early stages of tumour dissemination. We used minimal model of tissue comprising two cells to understand reorientation of internal polarity of cells during EMT. We found that after EMT induction, cells undergo polarity reversal by repositioning their centrosome and thus reorientating nucleus-centrosome axis. This polarity reversal involves redistribution of cellular forces which primes them for cell separation after EMT. We also found evidence of polarity reversal at different stages of developing mouse embryo and this reversal was essential for scattering of resulting mesenchymal cells.

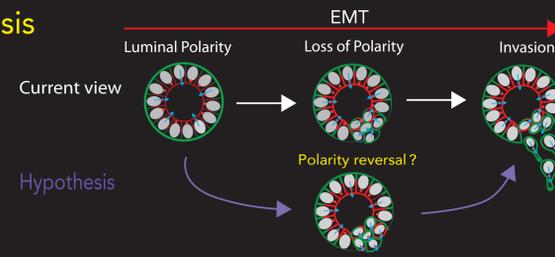
Abbreviations: MT- Microtubules, CCJ- Cell cell Junction, BB-Blebbistatin, NN- Intenuclear Distance, CC- Intercentrosomal distance
NN axis- Nucleus-nucleus axis, BM- Basement Membrane

Results

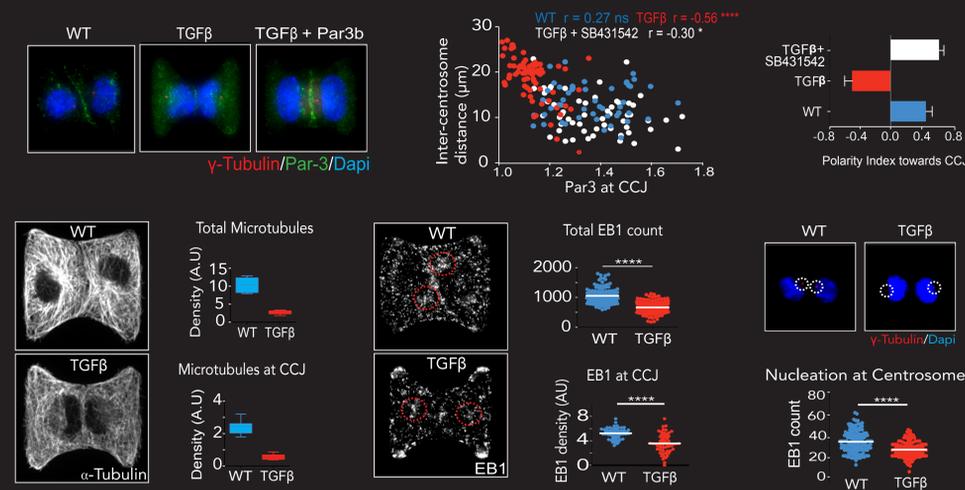
Polarity inversion during mouse development and in 3D acini



Hypothesis

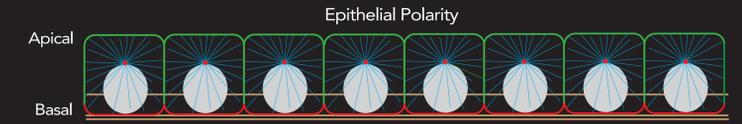


Par3 and MT reorganization for centrosome positioning during EMT

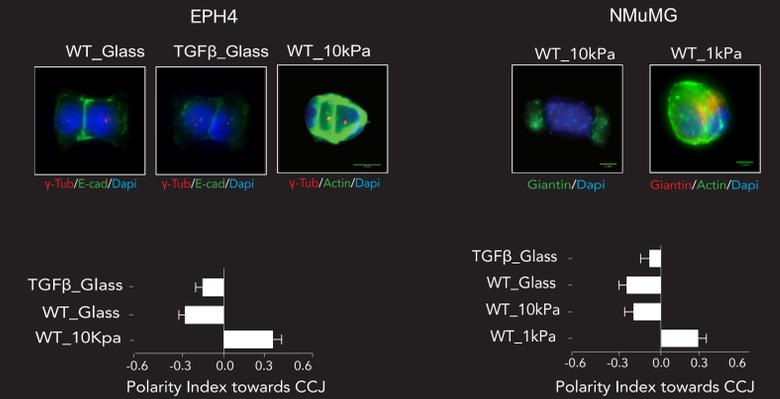


Introduction

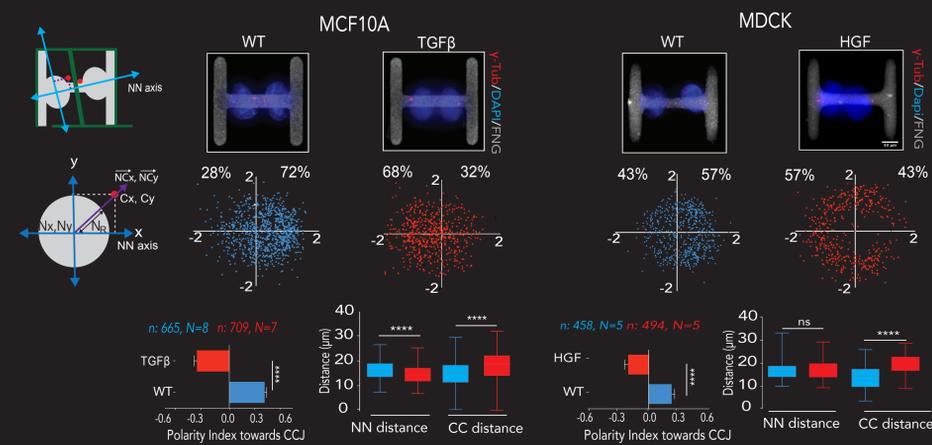
Centrosome acts as Microtubule organizing center (MTOC) and is often located at the geometric center of the single cell. In epithelial tissue, centrosome is preferentially located close to apical domain and thus defines Nucleus-Centrosome axis that is directed towards the lumen of the organ.



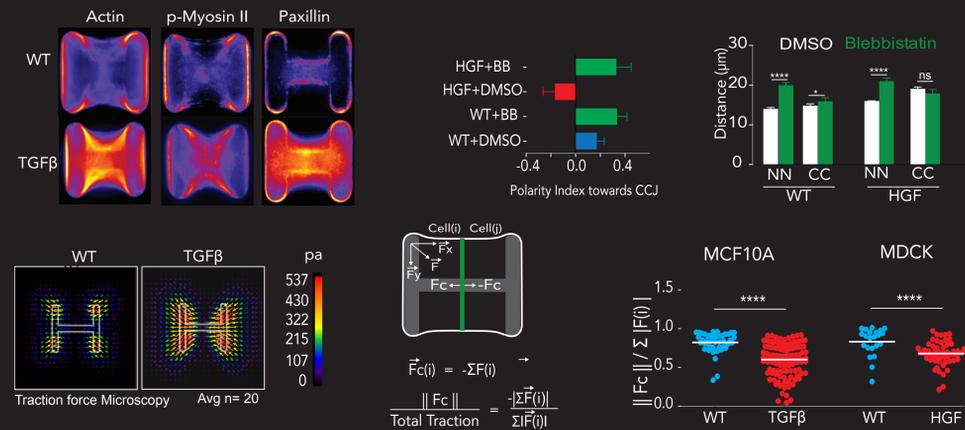
Polarity reversal is sensitive matrix rigidity



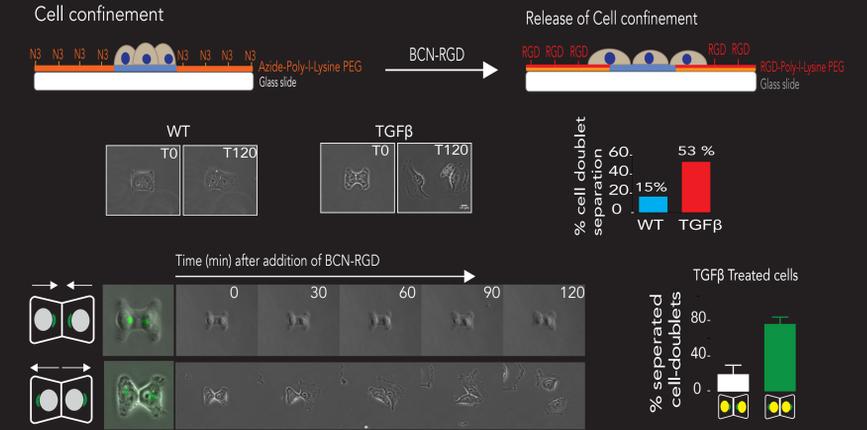
Polarity reversal occurs during EMT



Cellular force redistribution of cell-matrix and cell-adhesion forces



Polarity reversal initiates cell scattering during EMT

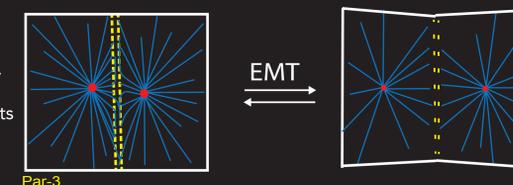


Conclusions

- EMT involves active reorganization of polarity by repositioning the centrosome and hence microtubule organization.
- Polarity reversal was observed in mammary gland (MCF10A, EPH4, NMuMG) and kidney (MDCK) cells as response to EMT inducers.
- Polarity reversal could be initiated in the absence of external EMT inducer, by only increasing the matrix rigidity.
- Reduction of MT number and nucleation after EMT suggest centrosome position can be affected by MT number.
- Polarity reversal by centrosome repositioning is required for cell scattering after EMT, in metastatic-like events.

Working Model

Par-3 accumulation at CCJ controls centrosome offcentering towards cell-cell Junction. After EMT, Par-3 loss from CCJ causes centrosome repositioning to the center of the cell, which results in polarity reversal after EMT



Proposed mechanism for EMT

