YAP regulates cell mechanics by controlling cell-matrix interaction strength

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The extracellular matrix (ECM) is the non-cellular constituent of the tissues that, far from being an inert structural scaffold, provides biochemical and biomechanical cues that impact on cell behavior. Several reports have focused on the molecular systems by which the ECM interaction impacts on the Hippo signaling pathway to regulate YAP nuclear shuttling and its consequent co-transcriptional activity[1,2].

In the present work, we describe the mechanism by which the mechanotransducer YAP directly controls through its transcriptional activity both the deposition of extracellular matrix components and the assembly of the intracellular apparatus of cell-ECM interaction, the focal adhesions (FAs). In fact, by exploiting ChIP-seq technology and YAP mutants obtained by CRISPR/Cas9 targeted approach, we unveil a number of targets of YAP-DNA binding activity that lead to the formation of membrane complexes devoted to the interaction with ECM including various integrin subunits like ITGA1, ITGA4, ITGAV and ITGB1, talin2, cadherins and catenins. At the same time, YAP binds DNA elements connected to the activation of genes encoding for ECM structural proteins like versican, collagens, laminins, fibronectin and osteonectin or involved in the processing of ECM components, like hyaluronan synthase 3, connective tissue growth factor (CTGF) and metallopeptidases. As expected, YAP mutant clones underwent a substantial switch in the expression of genes involved in structural ECM composition and remodeling, thus leading to the complete absence of FAs. As a consequence, cells failed to spread, invade and migrate through the surrounding matrix, when challenged in 2D and 3D assays and lose the ability to spread and acquire the given shape, develop tension through the cytoskeleton and exert force against the surrounding ECM.

Consistent with the model of YAP acting as a master of cell-ECM interaction, cell biophysical parameters were partially recovered by the re-expression of transcriptionally active YAP or ITGAV integrin subunit in conjunction with ITGB3 subunit, two of the proteins being more affected in YAP-defective cells[3].

In conclusion, YAP functions as the principal regulator of cell-matrix interface, being able to control the expression of crucial genes involved in the composition and arrangement of the extracellular environment, together with key components of cell mechanosome.

References:

[1] D. Mosqueira, S. Pagliari, K. Uto et al. (2014), ACS Nano. 8(3):2033-47

[2] NG. Kim and BM. Gumbiner (2015), J Cell Biol. 210(3): 503–515

[3] G. Nardone, J. Oliver De La Cruz et al. (2017), Nat Comm. DOI: 10.1038/ncomms15321

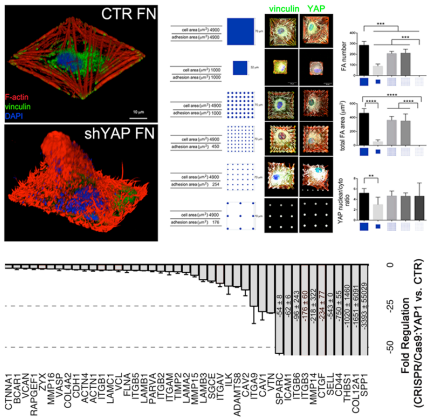

Figure 1. YAP depletion causes cell-ECM disruption. YAP activity is controlled by cell area independently of FA formation. YAP depletion results in decreased ECM and FA gene expression.

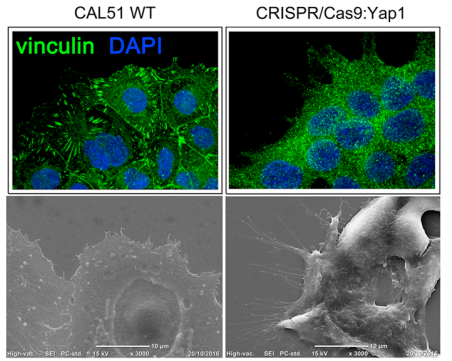

Figure 2. YAP-depleted cells lose the grip on ECM and fail to spread

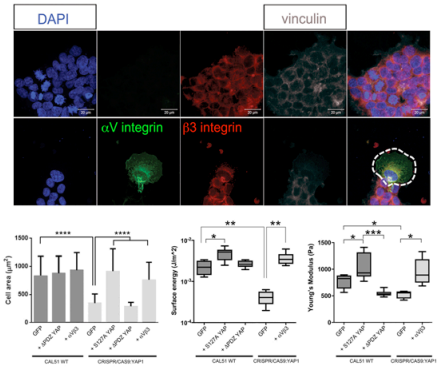

Figure 3. Re-expression of components of the Integrin-FA system partially restores the spreading and biomechanics of YAP-depleted cells.

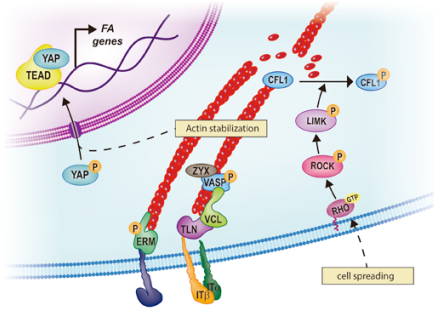

Figure 4. Cell spreading triggers RhoA/ROCK activation and YAP shuttling to the nucleus where it directly activates FA and ECM genes.