

Reduced RhoGDI2 expression disrupts centrosomal functions and promotes mitotic errors

Mudrika Tripathi¹, Jerome Willems¹, Nancy Garbacki¹, Marianne Fillet², Alain Colige¹, Christophe Deroanne¹

¹Laboratory of Connective Tissues Biology, GIGA-Cancer, University of Liege, Liege, Belgium

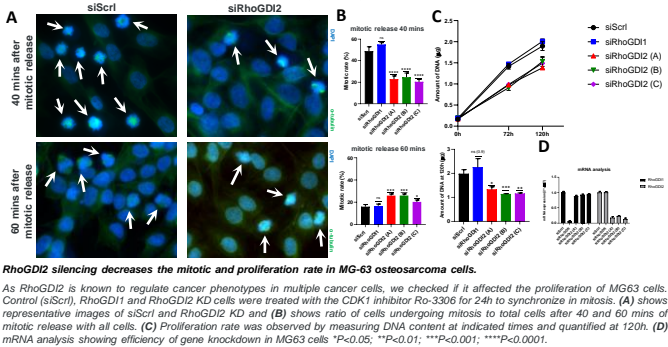
²Laboratory for the Analysis of Medicine, CIRM, University of Liege, Liege, Belgium



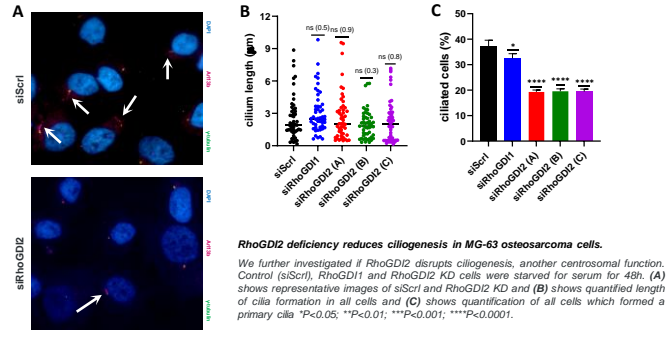
INTRODUCTION
RhoGDI2 is one of the three RhoGDI proteins that regulate nearly 20 RhoGTPases. Through RhoGTPases, RhoGDIs control a wide variety of signaling pathways to regulate actin and microtubule cytoskeleton, cell cycle progression, immune response and transcriptional regulation. RhoGDI2 is differentially expressed in many cell types and tissues, including cancer where its expression has been correlated to either good or bad prognosis depending on the cancer type and stage. Here, we knockdown (KD) RhoGDI2 expression in MG-63 osteosarcoma cells and NK-92 (natural killer) cells in order to better understand the dual function of RhoGDI2 in cancer. We also compare RhoGDI2 KD with RhoGDI1 KD to understand the functional differences between the two proteins. We show that RhoGDI2 KD disrupts key centrosomal functions, helping both cancer and immune cells, thereby highlighting its dual role in cancer.

RESULTS

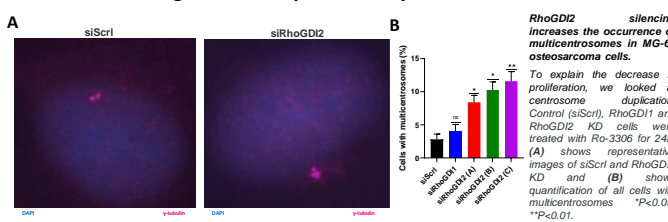
1. RhoGDI2 silencing negatively impacts proliferation.



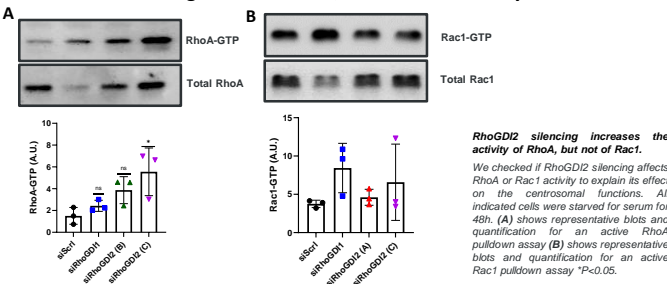
4. RhoGDI2 deficiency reduces ciliogenesis.



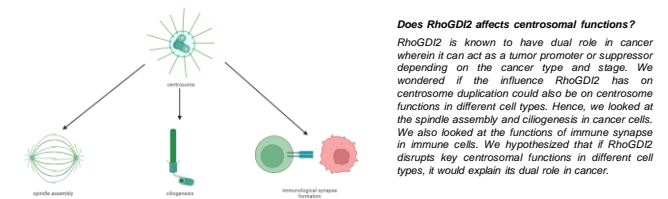
2. RhoGDI2 silencing increases supernumerary centrosomes.



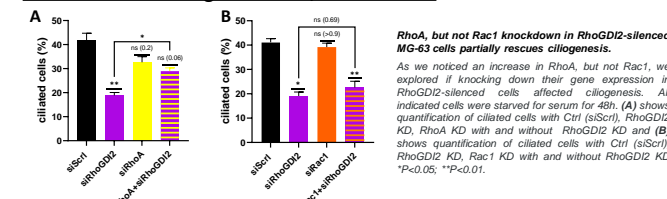
5. RhoGDI2 silencing increases RhoA, but not Rac1 activity.



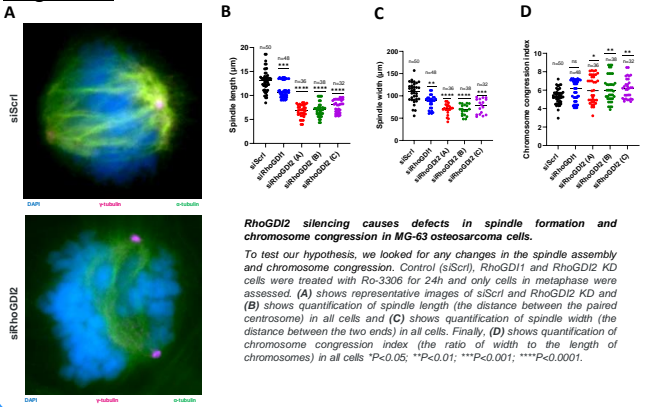
Does RhoGDI2 affects centrosomal functions?



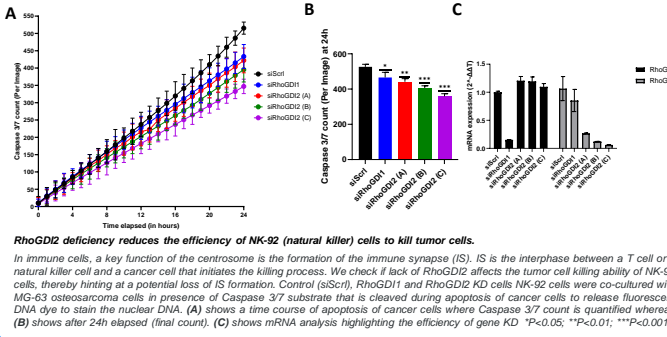
6. Ciliogenesis is partially rescued in RhoGDI2-silenced cells upon concomitant silencing with RhoA, but not Rac1.



3. RhoGDI2 silencing causes errors in spindle assembly and chromosome congression.



7. RhoGDI2 silencing reduces tumor killing ability in immune cells.



CONCLUSIONS

Our data clearly shows that RhoGDI2 plays a significant role in different functions of centrosomes in both cancer and immune cells. Centrosomal aberrations are commonly found in many human cancers, including osteosarcoma. RhoGDI2 may act as a tumor promoter by aiding centrosomal functions in cancer cells. In addition to its role in cancer cells, RhoGDI2 is highly expressed in natural killer (NK) cells where we show that it also regulates a key centrosomal function. NK cells are increasingly being used for cancer immunotherapy which is considered to be one of the most promising approaches for treating cancers. By aiding the tumor killing ability of NK cells, RhoGDI2 may act as a tumor suppressor, thereby playing a dual role in cancer.

Contact: mtripathi@uliege.be

