FINAl SUMMARY REPORT

The main objective of this project was to characterize the physiological function of the new cell cycle kinase Mastl in mammals, and explore its potential as a new target for cancer therapy.
Mastl, also known as Greatwall, was originally identified in *Drosophila*, in 2004, as a protein required for mitosis. Since then, most studies on this protein have been performed either in *Drosophila* or in *Xenopus* extracts. It was found that the main role of this kinase is to inhibit Protein Phosphatase 2 A (PP2A), when it is in complex with the B55 family of regulatory subunits. The inhibition of PP2A/B55 by Mastl is indirect, through the phosphorylation of two inhibitors of PP2A, Ensa and Arpp-19, which are the only Mastl substrates identified to date.
We have generated the first genetic model of this protein in mammals. By using our conditional knockout of Mastl we have found that cells lacking Mastl cannot divide properly. In the absence of Mastl cells have condensation problems and are not able to segregate their chromosomes. This collapse prevent those cells to divide their duplicated DNA content equally between the two daughter cells and, therefore, impairs cell proliferation.
The antiproliferative function of Mastl opens up the possibility of targeting Mastl as a new therapeutic approach for cancer treatment. The next step is to find the tumoral context in which inhibition of Mastl would have therapeutic benefit. One of the therapeutic advantages that Mastl offer, in contrast to other mitotic proteins, is that it acts by blocking the tumor supressor PP2A. This implies that inhibition of Mastl could, at the same time, impairs cell division and reactivate PP2A, a tumor suppressor that inhibits many oncogenic pathways involved in cancer progression. Interestingly, elimination of Mastl in vivo in young mice compromised survival, due to massive proliferation defects. However, only mild alterations were found when we deleted Mastl in adult mice, predicting low toxicity in potential Mastl-based therapies. Moreover, our preliminary data suggest a role for Mastl in DNA cohesion and DNA damage repair. These findings also have implications for the use of Mastl as a therapeutic target, since elimination of Mastl could be beneficial in DNA damage-based therapies. Additionally, we have found that high expression of Mastl correlates with poor prognosis in breast tumors.

This work has placed Mastl/Greatwall as a new potential target for cancer treatment. Current efforts are directed to identify those tumors that would respond to Mastl inhibition-based therapies. Moreover Mastl could also be useful as a prognostic factor in breast tumors, and, probably, in other tumor types. These findings significantly contribute to the development of novel targeted therapies and biomarkers for cancer treatment.

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Publications:

Álvarez-Fernández, M., Sánchez-Martínez, R., Sanz-Castillo, B., Gan, P.P., Sanz-Flores, M., Trakala, M., Ruiz-Torres, M., Lorca, T., Castro., A. and Malumbres, M. (2013) Greatwall is essential to prevent mitotic collapse after nuclear envelop breakdown in mammals. *Proc. Natl. Acad. Sci. USA* **110**, 17374-17379. [PMID: 24101512]

Álvarez-Fernández, M. and Malumbres, M. (2014) Preparing a cell for nuclear envelope breakdown: Spatio-temporal control of phosphorylation during mitotic entry. *Bioessays* **36**, 757-765. [PMID: 24889070]

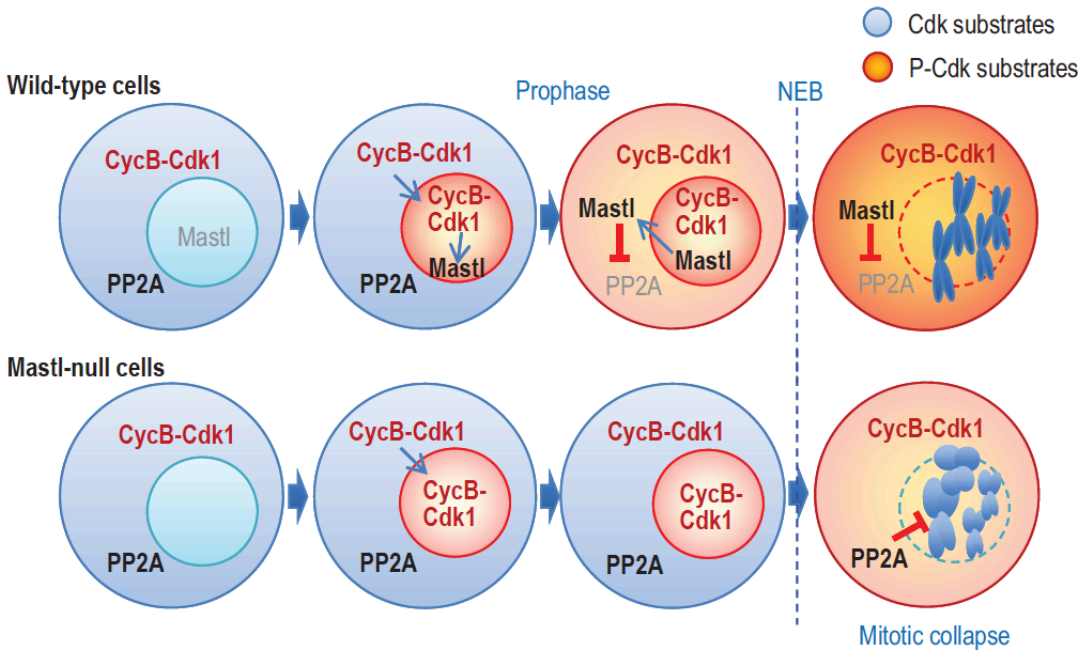

Figure 1. Model for Mastl function in the cell division process (mitosis) in mammalian cells. (*Alvarez-Fernández et al., 2013*).