Spanish researchers discover how left-right information is integrated to ensure correct organ positioning

- A transient wave of small molecules establishes a temporary window that ensures correct heart positioning
- These results, published in Developmental Cell, explain how asymmetry is achieved in the developing embryo.

Scientists from the Instituto de Neurociencias CSIC-UMH in Alicante, Spain, under the supervision of Professor Angela Nieto, have discovered the molecular mechanism that ensures the right equilibrium needed in left-right signaling cascade during development for the correct leftward positioning of the heart.

Previous findings of the research group published in Nature in 2017, have shown that for the heart to move to the left from it is initial central position, it receives cells from both the left and right-hand sides of the embryo, but more cells are travelling from the right. This establishes asymmetric forces that push the heart to the left. However the question remained as to how this left-right asymmetry in cell contribution was established.

The answer to this question is now unveiled in the work published in Developmental Cell. “We have now found that during a very short time window a wave of small molecules called microRNAs travel all along the left-hand side of the embryo, attenuating the signals that send cells to the heart and, therefore, more cells travel from the right-hand side towards the midline, pushing the heart to the left” explains the first author of the work, Luciano Rago. “An interesting fact is that this mechanism seems to be conserved in all vertebrates, including humans, as we found that it is

present in zebrafish, chicken and mouse embryos" highlights Professor Nieto.

This work is an important contribution to the developmental biology field, because it explains the temporal and dynamic regulation of the main players governing organ positioning, and integrates previous knowledge and new findings in left-right determination in the embryo.

Until 2017 it was believed that left-right asymmetry was mainly established by an instructive information coming from the left, that was suppressed on the right. However, thanks to their previous work and the one published now in Developmental Cell, Professor Nieto's group describe that the integration of information coming from both sides of the embryo is key to establish the final position of the heart and its proper development.

The proper position of the heart, with its posterior pole pointing to the left is fundamental for a correct concordance of the heart with the circulatory system. Around 50% of congenital malformations detected at birth in humans are heart malformations, and many of those are related to defects in heart positioning. Thus, the description of the mechanism that ensures its correct position helps to better understand cardiac malformations.

Rago L., Castroviejo N., Fazilaty H., Garcia-Asencio F., Ocaña O.H., Galceran J., Nieto M.A. *MicroRNAs establish the right-handed dominance of the heart laterality pathway in vertebrates*. Developmental Cell in press