MedicalXpress

New genetic findings explain how embryos form arms and legs

May 24 2018

The current understanding of limb and lung development in humans does not capture the full picture of the process, according to research published in *Nature* last week. This paper describes the importance of novel genes for limb development, and shows how perceived wisdom about the process was incomplete.

An international group of clinicians and researchers from Singapore, Turkey, France, Portugal and India, studied five families with either limb malformations, or tetra-amelia syndrome that is characterised by the absence of lungs and all four limbs. They found that mutations in the RSPO2 gene lead to incomplete limb development.

Until now, the RSPO proteins were believed to only work with their receptors called LGRs. Together, RSPO and LGRs were thought to allow limb formation by blocking two key enzymes ZNRF3 and RNF43.

Or so we thought.

The team then studied mice lacking all three LGRs required for RSPO2's function, and found that contrary to what was expected they still developed limbs and lungs normally. This indicates that RSPO2 does not need LGRs—disproving the established understanding of how this is happening.

"Our results establish that even without the LGR receptors, RSPO2, can bind to other molecules and constitute a master switch that governs limb

development," says Dr. Emmanuelle Szenker-Ravi, a co-first author of the study based at Agency of Science, Technology and Research's (A*STAR) Institute of Medical Biology (IMB) in Singapore.

Together with collaborators in Belgium, the team went on to check this same pathway in frog models, and confirmed that the absence of RSPO2 prevents limb development. Interestingly, they showed for the first time the importance of ZNRF3 and RNF43 for proper limb development. Indeed, the biggest surprise came when they removed both ZNRF3 and RNF43, and discovered that frogs would grow extra arms and legs.

The lead author Professor Bruno Reversade, who is based at A*STAR in Singapore, speculates whether this may also help explain why some animals such as salamanders can regrow limbs after amputation. "We were puzzled by these results as this pathway is thought to be largely understood," Dr. Reversade says. "As ever, unexpected discoveries allow one to challenge the prevailing dogma and better capture the complexity of biology."

Beyond the formation and regeneration of limbs which have strong applications in regenerative medicine, the teams' findings also bear important implications in cancer research. The very same genes RSPO2, RNF43 and ZNRF3 are often found to be mutated and cause colorectal cancer. Thus the knowledge of how humans form limbs might provide new therapeutic options for cancer patients.

More information: Emmanuelle Szenker-Ravi et al. RSPO2 inhibition of RNF43 and ZNRF3 governs limb development independently of LGR4/5/6, *Nature* (2018). DOI: 10.1038/s41586-018-0118-y

Provided by Agency for Science, Technology and Research (A*STAR),

Singapore