Institute of Medical Biology
A*STAR

MEDIA RELEASE
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22 May 2018

New genetic findings explain how embryos form arms and legs

New discovery revises biologists' understanding of how limbs and lungs develop in humans.

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. (Image below)

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.

For more information, please refer to the paper, “RSPO2 inhibition of RNF43 and ZNRF3 governs limb development independently of LGR4/5/6” published in *Nature* on 16 May 2018.

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For media queries and clarifications, please contact:

Ms Sunanthar Lu
Senior Officer, Corporate Communications
Agency for Science, Technology and Research (A*STAR)
+65 6517 1966
Sunanthar_Lu@hq.a-star.edu.sg

About A*STAR's Institute of Medical Biology (IMB)
IMB is one of the Biomedical Sciences Institutes of the Agency for Science, Technology and Research (A*STAR). It was formed in 2007, with a mission to study mechanisms of human disease in order to discover new and effective therapeutic strategies for improved quality of life.

IMB has 20 research teams working in three primary focus areas - stem cells, genetic disease, and skin biology. The teams work closely with clinical collaborators as well as industry partners, to target the challenging interface between basic science and clinical medicine. IMB's strategic research topics are targeted at translational research to understand the mechanisms of human disease so as to identify new strategies for disease amelioration, cure and eradication and to improve health and wellbeing. Since 2011, IMB has also hosted the inter-research institute Skin Biology Cluster platform, and leads major strategic funding programs in rare genetic diseases and in skin biology. In 2013, IMB became a founding institute of the Skin Research Institute of Singapore. For more information about IMB, please visit www.imb.a-star.edu.sg.

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About the Reversade Laboratory
Dr Bruno Reversade, a human geneticist holds a Research Director position at IMB and IMCB. He is leading A*STAR's strategic programme on Genetic Orphan Diseases. He is an adjunct Professor of the Department of Paediatrics at the National University of Singapore, a joint scientist at KKH, a distinguished Professor of Genetics at Koç University in Istanbul (Turkey) and Professor of Genetics at the Amsterdam Reproduction & Development Alliance Institute at AMC / VuMC in the Netherlands. He is also a Fellow of the Branco Weiss Foundation based at ETH in Switzerland, and was the first recipient of the A*STAR Investigatorship, and the first EMBO Young Investigator based outside Europe. For more information about Dr Reversade's laboratory, visit www.reversade.com.