

PRESS RELEASE

IMB Scientists Identify Key Event for Sex Determination

Mainz, November 2012. *Scientists at the Institute of Molecular Biology (IMB) in Mainz have identified a protein essential for initiating the development of male sex organs. Loss of the gene *Gadd45g* results in complete sex reversal of male mice, making them appear female. The researchers' finding uncovers a novel signalling cascade, which acts early in development to determine the gonads in males. This discovery sheds light on the genetic network that controls how embryos develop as males or females. The research has just been published in the high-impact journal *Developmental Cell*.*

Research carried out in the laboratory of IMB Director Professor Christof Niehrs uncovered that the deletion of just one gene, *Gadd45g*, results in male mice with external genitalia that are indistinguishable from those of female mice. Furthermore, the internal reproductive organs of the mutant male mice look like those of females, indicating that a complete sex reversal has occurred. Says Christof Niehrs, "*when breeding *Gadd45g* mutant mice we were puzzled why we got only females, until we discovered that some of these females actually carry a Y-chromosome.*"

The researchers further showed that *Gadd45g* exerts its effect by regulating signalling cascades that control the gene *Sry*, which had previously shown to be a master regulator of male sex development. This study both identifies a new role for *Gadd45g* and suggests a novel signalling pathway that could have important implications for research into disorders of sexual development.

For male sex organs to develop correctly, it is essential that the gene *Sry* is expressed at high levels within a very narrow timeframe in the embryo. The group of Christof Niehrs has now shown that *Gadd45g* is expressed in a pattern highly similar to that of *Sry*. The *Gadd45g* gene is, however, active just before *Sry* is turned on. Importantly, in mice lacking *Gadd45g*, the *Sry* gene is not expressed correctly. This indicates that *Gadd45g* controls the expression of this master regulator and, in turn, male development.

The scientists also provide a possible mechanism by which *Gadd45g* regulates *Sry*. Their model suggests that *Gadd45g* binds to and activates key signalling proteins, such as p38, which activate the transcription factor Gata4. When active, this factor binds to and activates the *Sry* gene. Similar results are co-published in the same issue of *Developmental Cell* by the group of Andy Greenfield in the UK. "*As outsiders to the field of sex determination we were surprised by how little was known about the regulation of *Sry* on the molecular level. Our work is a leap forward in the understanding of this fundamental process*", says Niehrs.

Original reference: Mathias S Gierl, Wolfram H Gruhn, Annika von Seggern, Nicole Maltry and Christof Niehrs (2012). *Gadd45g* functions in male sex determination by promoting p38 signaling and *Sry* expression. *Developmental Cell* **23**(5):1032-42

Webpage of Prof. Niehrs' Research Group at IMB: www.imb-mainz.de/research-at-imb/niehrs

Institute for Molecular Biology gGmbH (IMB)

The Institute of Molecular Biology gGmbH (IMB) is a new research centre in the life sciences, which was established in March 2011. Research at IMB concentrates on three cutting-edge research areas: Developmental Biology, Epigenetics and DNA Damage Response. The research centre is a prime example of successful collaboration between public authorities and a private foundation: The Boehringer Ingelheim Foundation has dedicated 100 million Euro for a period of ten years to cover the scientific running of IMB, while the state of Rhineland-Palatinate provided 50 million Euro for the construction of a modern building to house IMB. For more information about IMB please visit: www.imb-mainz.de.

Boehringer Ingelheim Foundation

The Boehringer Ingelheim Foundation is an independent, non-profit organisation committed to the promotion of the medical, biological, chemical and pharmaceutical sciences. It was established in 1977 by Hubertus Liebrecht, a member of the shareholder family of the company Boehringer Ingelheim. In addition to various awards for up-and-coming scientists at the University of Mainz, the foundation has endowed 100 million euros over a period of ten years to finance the scientific running of the Institute of Molecular Biology (IMB) at the University of Mainz. For more information about the foundation and its programmes please visit: www.boehringer-ingelheim-stiftung.de.

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