Scientists identify key event for sex determination

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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 signaling 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 signaling 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 signaling 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 signaling 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.

More information: Gierl, M.S. et al. (2012), Gadd45g functions in male sex determination by promoting p38 signaling and Sry expression, *Developmental Cell* 23(5):1032-42. doi:10.1016/j.devcel.2012.09.014

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