Scientists uncover gene 'architects' responsible for body's blueprint

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Associate Professor Anne Voss (right) and Associate Professor Tim Thomas led the research team from the Walter and Eliza Hall Institute in Melbourne, Australia.Previous work by the research team from the Walter and Eliza Hall Institute showed that the protein MOZ could relay external 'messages' to the developing embryo, revealing a mechanism for how the environment could affect development in very early pregnancy. Credit: Walter and Eliza Hall Institute

Researchers have identified two key proteins that act as genetic 'architects', creating the blueprint needed by embryos during the earliest stages of their development.

Previous work by the research team from the Walter and Eliza Hall Institute in Melbourne, Australia, showed that the protein MOZ could relay external 'messages' to the developing embryo, revealing a mechanism for how the environment could affect development in very early pregnancy.

Dr Bilal Sheikh, Associate Professor Tim Thomas, Associate Professor Anne Voss and colleagues have now discovered that MOZ and the protein BMI1 play opposing roles in giving developing embryos the set of instructions needed to ensure that body segments including the spine, nerves and blood vessels develop correctly and in the right place.

Associate Professor Voss said the study revealed that the proteins tightly regulated Hox gene expression in early embryonic development. "In very early development, when the embryo is still just a cluster of dividing cells, the embryo must become 'organised' so that the body tissues and organs develop correctly, with everything in its right place," Associate Professor Voss said.

"The embryo is organised along an 'axis' from head to tail, and a standard pattern of development is established that subdivides the body into segments, with each segment responsible for producing specific aspects of tissues and organs, including the vertebral column, spinal cord and nerves.

"We showed that the proteins MOZ and BMI1 were important for initiating activation of the Hox genes - section by section - providing the blueprint the developing organism needs for proper development."

Associate Professor Voss said that, though they worked together, MOZ and BMI1 played opposing roles. "We discovered that MOZ and BMI1 were important for initiating and correctly timing Hox gene expression, ensuring the genes were activated at the right time and in the right place," she said.

MOZ was responsible for activating the genes, while BMI1 prevented Hox genes being switched on prematurely, Associate Professor Voss said.

She said the research also showed that significantly reducing Hox gene expression still allowed normal development, as long as the timing and location of expression were correct.

"We found that if the Hox genes were activated too early or late, it had significant repercussions for the developing embryo, such as malformations of the spine," Associate Professor Voss said. "Interestingly, we also found that producing an 'accurate' amount of MOZ or BMI1 in developing embryos was not nearly as important for correct development as when and where Hox genes were activated."

Importantly, MOZ and BMI1 could provide a mechanism to transmit signals from the environment to the developing embryo, with potentially devastating consequences.

"We know that Hox genes can be directly affected by too much vitamin A, which can cause severe deformities in the embryo," Associate Professor Voss said. "Substances or environmental challenges that impact MOZ or BMI1 expression could affect when and where Hox genes are expressed, causing defects in the developing embryo."

Dr Anne Voss said the research team's discovery overturned a decades-long belief about embryonic development. "A lot of what we know about

embryonic development and how it is controlled was learned from studies of fruit flies," Associate Professor Voss said. "In this study we showed a key difference; two molecules that have only a maintenance role in fruit flies are indispensible for initiating the blueprint in mammalian development."

The research was published today in the journal *Proceedings of the National Academy of Sciences* and was funded by the National Health and Medical Research Council and the Victorian Government. Dr Sheikh was a PhD student at The University of Melbourne during part of this research study.

More information: MOZ and BMI1 play opposing roles during Hox gene activation in ES cells and in body segment identity specification in vivo, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1422872112

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