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The *H19* locus: regulatory function of an imprinted non coding RNA in embryonic development

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Background

Although the *H19* gene was discovered in 1984, its precise function is still relatively poorly understood. It is located on mouse chromosome 7, close to the *Igf2* (insulin-like growth factor 2) gene, in an imprinted locus. The maternal allele expresses a 2.3kb non coding RNA, as well as a micro RNA, the miR-675. We showed that *H19* acts as a transregulator of an imprinted gene network (IGN) involved in growth control of the embryo [1]. A recent study described that the miR-675 is exclusively expressed in the placenta during development, where it controls growth probably by downregulating the expression of *Igf1r* [2]. However, this micro RNA is unable to control the IGN in the embryo, control that appears therefore to be exerted by the full-length form of *H19*. The main goal of our work was to understand molecular mechanisms that drive this control of the IGN by *H19*.

Materials and methods

Loss-of-function ($H19^{\Delta 3}$) and gain-of-function ($H19^{Tg}$) mouse mutants were used. $H19^{\Delta 3/+;Tg}$ females were crossed with *Mus musculus molossinus* (JF1) *wt* males. Polymorphisms between molossinus and domesticus mice allow to distinguish the maternal from the paternal allele. $H19^{\Delta 3/+mol}$, $H19^{+dom/+mol}$ and $H19^{-/+mol;Tg}$ E14.5 embryos were collected from this cross in order to dissect limb muscles, or produce primary mouse embryonic fibroblasts (MEF) for ChIP and RIP (RNA immunoprecipitation) experiments.

Results

We first investigated the imprinting status of the IGN and observed that *H19* controls by a *trans* mechanism the imprint of the *Igf2* gene, but not of other genes of the IGN. We performed RIP experiments in MEF and identified the MBD1 protein as a partner of the *H19* RNA. We also observed that some genes of the IGN, including the *Igf2* gene, are overexpressed both in $Mbd1^{-/-}$ and $H19^{\Delta 3/+mol}$ MEF. This suggests that *H19* may act on this network because of its interaction with the MBD1 protein. By ChIP experiments, we showed that MBD1 indeed binds to the *Igf2* gene and to other common targets of both *H19* and MBD1. Interestingly, this binding is lost in $H19^{\Delta 3/+mol}$ MEF. This indicates that *H19* is necessary for the recruitment of MBD1 to its targets.

Conclusion

These results strongly suggest that the control of the expression of some genes of the IGN, including the *Igf2* gene, could be exerted through an interaction of the *H19* full-length RNA with the MBD1 protein.

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