Msx1 and physiopathology of labial palatal cleft either isolated or combined with tooth agenesis

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Oral Dysmorphia 2007-2010
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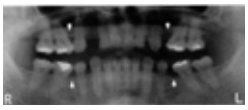
State of art and objectives of the study

Congenital oral malformations induce a major functional and aesthetic handicap. The present project on palate clefts, tooth agenesis and Msx1 gene associates clinical and experimental investigations.
Msx1 is involved in epithelio-mesenchymal interactions and is specific of oral tissues as demonstrated by phenotypes resulted from human Msx1 mutation and mice invalidated for Msx1 gene (figure 1). Msx1 acts by inducing cell proliferation and apoptosis.
In parallel, our group showed that Msx1 gene is submitted to bi-directional transcription, thus generating an antisense RNA complementary to the exon 2 that constitutes an additional level of gene expression regulation.


Vastardis et al., Nat Genet, 1996


Satokata & Maas, Nat Genet, 1994


Houzelstein et al., Mech Dev, 1997

Our project was divided into 3 axes:
-Establishment of an inducible Msx1 KI mouse line
-Regulation of Msx1 expression by its own antisense RNA
-Establishment of a transgenic mouse line overexpressing Msx1 in bone

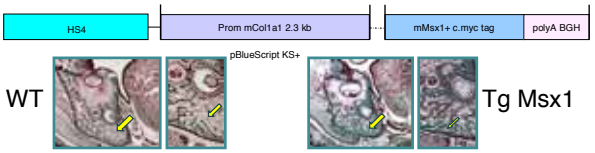
Results

-task 1:

Three recombinant ES cell clones were obtained. During the development of the project, a collaboration has been established with R. Maxson's lab in order to share the same animal model.

-task 2: The underlying mechanism of Msx1 antisense RNA was analysed in vitro and in vivo. Msx1 induced AS transcription whereas the excess of AS RNA decreased Msx1 mRNA half-life.
This variable Msx1 S/AS ratio was also found in two families carrying a mutation on Msx1 gene and presenting tooth agenesis.
Our results concerning the retro-control of Msx1 expression are summarized in the figure below.

-task 3: Msx1 overexpressing mice were obtained and presented an increase of bone volume.



Conclusion: Our hypothesizes concerning Msx1 as a oral bone trophic factor were confirmed by this study. Experiments are currently carried out to establish clinical applications for Msx1.

Impact / Publications

Concerning Msx1 and its antisense RNA expression :
- Petit S, et al, Autoregulatory loop of Msx1 expression involving its antisense transcripts. J Cell Physiol. 2009;220(2):303-10.
- Babajko S, et al, Msx1 expression regulation by its own antisense RNA: consequence on tooth development and bone regeneration. Cells Tissues Organs. 2009;189(1-4):115-21.
- Babajko S, et al, Transcriptional regulation of Msx1 natural antisense transcript. Cells Tissues Organs. 2011, in press

Concerning the two other axes of the project:
- van den Boogaard MJ, Babajko S et al, A new case of Cheilo-gnatho-palatoschisis with a MSX1 homeodomain mutation: The tentative role of sense – antisense and Nonsense mediated mRNA decay complex in the phenotypic expression of MSX1 (submitted)
-Senussi I, Méary F Nefussi JR, Petit S, Robert B, Berdal A, Babajko S. Msx1 involvement in dysmorphology and reparation of alveolar bone (in preparation)

Review publications (under invitation):

Bailleul-Forestier I., Molla M., Verloes A., Berdal A. The genetic basis of inherited anomalies of the teeth. Part 1 : Clinical and molecular aspects of non-syndromic dental disorders. Eur. J. Med. Genet., 51(4) : 273-291, 2008.
Bailleul-Forestier I., Molla M., Verloes A., Berdal A. The genetic basis of inherited anomalies of the teeth. Part 2 : syndromes. Eur J Med Genet. 2008, 51(5):383-408.

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