A Cure for Mice with X-linked Hypohidrotic Ectodermal Dysplasia

by

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I have been studying X-linked hypohidrotic ectodermal dysplasia (XHED) for about 20 years. From the start, simply because of how the condition is inherited, we knew that the gene involved must lie somewhere on the X chromosome - and that mutations in this would cause XHED. I have seen our collective understanding advance from a very preliminary suggestion as to whereabouts on the X chromosome the gene might lie through the isolation of the gene in the 1990s to an understanding of the protein encoded by the gene and how it interacts with the protein product of another gene (on human chromosome 2) in which mutations can also cause (non-sex-linked) HED. I was not expecting to see a cure for the condition - the gene has to function early in development, long before birth, for sweat glands and other ectodermal structures to form correctly - and so I was unprepared for the report in 2003 that a Swiss group had "cured" mice with the mouse equivalent of XHED, termed Tabby.

I am (slowly) preparing a book about ectodermal dysplasia, and so I wished to find out more about the team who had carried out this work. I visited Geneva last autumn to catch up with some friends, to have a short holiday with Jane, my wife, and to meet Drs Olivier Gaide and Pascal Schneider. I was given a warm welcome by these two researchers; both Olivier and Pascal went to a lot of trouble to explain their work to me.

In brief, it was already known that the EDA1 protein produced from the Tabby (Eda) gene, was required early in development so as to induce the correct formation of ectodermal appendages such as hair, teeth, sweat glands and the Meibomian glands of the eye. Gene therapy can be used in mice to achieve this, but Olivier and Pascal thought out a different approach. Instead of providing a replacement for the gene, they gave the mice treatment with a modified form of the corresponding protein molecule, altered so that it would be transported across the placenta in just the same way that certain maternal antibodies are passed across the placenta to the fetus. This modification to the protein also resulted in a greater capacity for the ectoderm to compensate for the absence of the correct protein. The mice could be (more or less) cured by giving the pregnant mouse two injections with the modified protein or by giving the newborn Tabby mice a single injection.

These investigations are a dramatic proof that the embryonic signalling required for the correct formation of sweat glands, teeth etc is only required to operate for a short time during a critical "window" in development. Before or after that window, even the correct gene product will not function. This is all very well for the mice, of course, but it is very difficult to predict how this might feed through to the real world of human families with

XHED. There are two particular difficulties to consider - important differences between man and mouse.

The first is that infant mice are born at a much earlier stage in development than are infant humans. A mouse pregnancy lasts just 20 days as opposed to 9 months in the human, and some of the features of the mouse Tabby mutation are restored only by treatment before birth, whereas for other features the "window" of opportunity lasts for a week or so after birth. Even so, it is clear that any really effective treatment in humans would probably have to involve several treatments, and all the treatments would have to be administered during the pregnancy. In humans, the development of hair and sweat glands would most likely require the correct protein on several occasions from about week 14 to perhaps week 20-22.

The second relevant difference between man and mouse is - very properly - that researchers are not allowed to inject developmentally powerful molecules into pregnant women just to see what happens. There are regulatory frameworks that restrict such activities; we must all have heard of thalidomide. If any progress was to be made in this direction, there would need to be further experimentation in a range of different animals, not just mice, and probably including cats, dogs and/or primates.

If such treatment was going to be applied to humans, it would be in a family where the gene mutation causing XHED was known, where the woman was willing to undergo prenatal diagnosis at about 11 weeks of the pregnancy to see if the fetus was male and affected, and who would be willing in that event to have one or several injections over the following 2-3 months of a modified form of the XHED gene product, ectodysplasin A1, in the hope that it would resolve the child's XHED without itself causing any problems. I do think this could possibly work out well, but whether or not many prospective mothers would want to go through these procedures I simply do not know. Furthermore, there is a long way to go before anyone could possibly be in a position to carry out such an experiment on humans.

I have enormous respect for the ability and enthusiasm of Olivier and Pascal, but they are also thoroughly realistic and they are not expecting to apply their experimental treatments to humans in the near future.

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