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New mouse-human modeling system enables study of disease development in vivo

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Whitehead Institute researchers have created a new mouse-human modeling platform that could be used to study neural crest development as well as the modeling of a variety of diseases, including such cancers as melanoma and neurofibromatosis.

"We introduced human committed stem cells at the right stage into the mouse embryo in utero and had them integrate into developing tissues," says Whitehead Founding Member Rudolf Jaenisch. "The results are encouraging and provide a proof of principle—an important first step toward the goal of generating mice that carry disease-relevant human cells in the relevant tissue."

Resulting mouse-human chimeras would fill an important gap in disease research, as existing models do not accurately mimic certain diseases and disease states. Cancer is frequently studied by implanting cells from human tumors into mice, but this approach fails to provide insight into solid tumor initiation and progression. Complex diseases with long latencies, including Alzheimer's and Parkinson's, can be partially modeled using induced pluripotent stem cells (iPSCs). However, short-term culture in a dish cannot capture the lengthy process of disease progression in a living organism.

To overcome these limitations, scientists in Jaenisch's lab advanced a method he initially used back in 1985 to create mouse-human chimeras. In the current research, the team, led by postdoctoral researcher Malkiel Cohen, injected mouse embryos in utero with neural crest cells (NCCs)

derived from human embryonic stem cells (hESCs) and human iPSCs. The researchers theorized that, if successful, the implanted NCCs would differentiate and integrate seamlessly into their host mice.

NCCs are multipotent cells that give rise to a limited lineage, including the peripheral nervous system and melanocytes that produce the pigment found in skin and hair. During development, NCCs migrate through the embryo. The implanted NCCs, which had been labeled with green fluorescent protein (GFP), exhibited similar migration patterns. Approximately 27% of the implanted embryos had GFP-labeled NCCs present during development, a frequency similar to what Cohen and Jaenisch saw in a parallel experiment with mouse-mouse chimeras.

Because the NCCs were implanted into white mice lacking pigment, any hairs pigmented by cells arising from the donor NCCs are noticeably darker. Approximately 35% of the resulting mice had isolated black hairs on their heads, indicating that the implanted NCCs had successfully differentiated and integrated into the host mice. Although a similar percentage of mouse-mouse chimeras had black hairs, those mice had expanded contribution of dark hairs than the scant ones present in the mouse-human chimeras' coats.

Both Cohen and Jaenisch are now working to improve the rate of integration.

"The key barriers for human cells to functionally integrate into the mouse embryo are the significant differences in the biology of the human donor and the rodent host," says Cohen, whose work is described online this week in the *Proceedings of the National Academy of Sciences (PNAS)*. "Our next step will be to manipulate the mice and/or the injected human cells in order to allow better matching between the hosts and the donor human cells, hence to get better contribution by the cells successfully introduced into the embryo."

More information: Human neural crest cells contribute to coat pigmentation in interspecies chimeras after in utero injection into mouse embryos, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1525518113