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FRONT MATTER: DISCOVERY

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Zika-related microcephaly in experimental models*

Comment on: Cugola F, et al. The Brazilian Zika virus strain causes birth defects in experimental models. Nature 2016; 534:267-71; http://dx.doi.org/10.1038/nature18296

First discovered in 1947, the Zika virus is an arbovirus of the *Flaviviridae* family, that has not been reported to cause human disease until 2007 when the first outbreak took place in the Yap State, Micronesia. Patients referred fever, joint pain, cutaneous rashes and conjunctivitis. A few years later, in 2014, another outbreak in French Polynesia highlighted the relevance of the new agent that may easily spread throughout the globe, especially because of the worldwide prevalence of its vector, the mosquito *Aedes egypt*. In 2015, the virus arrived in Brazil infecting a huge amount of people, but this time associated with more dramatic features: babies born with microcephaly and adults with Guillain-Barré syndrome. Thus, the exponential raise in the number of cases of Zika infected patients has become an important burden for public health in Brazil since 2015. Actually, the most recent report of the Brazilian Ministry of Health indicates 7.534 notified cases, which 1.384 were confirmed. In fact, the first baby born with Zika-related microcephaly was reported in the USA recently. The numbers are still rising, and the threat to other countries, both in South and North America, has become a major concern. Although the virus had been present in brain specimens of microcephaly babies, direct causal relationship with microcephaly had yet to be uncovered, as other factors, i.e., nutritional state, co-infection and the previous exposure, specially to Dengue virus had to be ruled out.

In this context, our group have intensively worked on mouse experimental models in order not only to investigate this possibility, but also to establish a model, through which researchers could uncover so many other aspects of the Zika infection. Moreover, this would of great relevance in pre-clinical approaches for a vaccine. Recently, we and 2 other groups have published our findings showing that in fact the virus is able to cross the placental barrier, reach fetuses´s central nervous system and cause microcephaly.[1-3] It is worthy to mention that, whereas the 2 other groups used drug-induced IFN-αR (Interferon α Receptor) blockade, or IFN-αR deficient animals, we infected SJL wild type animals with high doses of the of the virus (Fig. 1). Interestingly, C57Bl/6 mice were completely resistant to fetal infection, as we were neither able to detect the virus in the brains of the pups, nor cortical reduction. This highlights the importance of the maternal immune *status*, as the robust anti-viral response of this strain, mostly relying on Type-I interferons, may account for viral elimination. In fact, it has been elegantly shown that trophoblast cells constitutively secrete Type III interferon-λ, restraining viral growth and rendering nearby cells refractory to infection. Despite differences in the approaches, all researches had similar results, with reduced brain size, increased apoptotic rate of cortical layer and microcephaly associated with intra-uterine restriction growth or fetal demise. These findings are in fact highly consistent with several clinical findings in human newborns, finally establishing the causal relationship between Zika and microcephaly. However, we may speculate that the infection during pregnancy results in a wider range of symptoms, evidencing a probable Zika-related congenital syndrome, and even non-microcephaly babies from infected mother must be accompanied in order to asses further problems.

Using neurospheres and brain organoids, our results were in accordance with several others, showing that neuronal precursor cells are easy target for Zika replication.[4,5] The reason is because these cells have a high expression of the AXL receptor (receptor of the TAM tyrosine kinase family), necessary for Dengue and Zika cell invasion. In fact, using a Brazilian Zika isolate, we demonstrated that this strain is more aggressive concerning its ability to induce damage to neuronal precursor cells and neurospheres. We reported a significant reduction in the cortical

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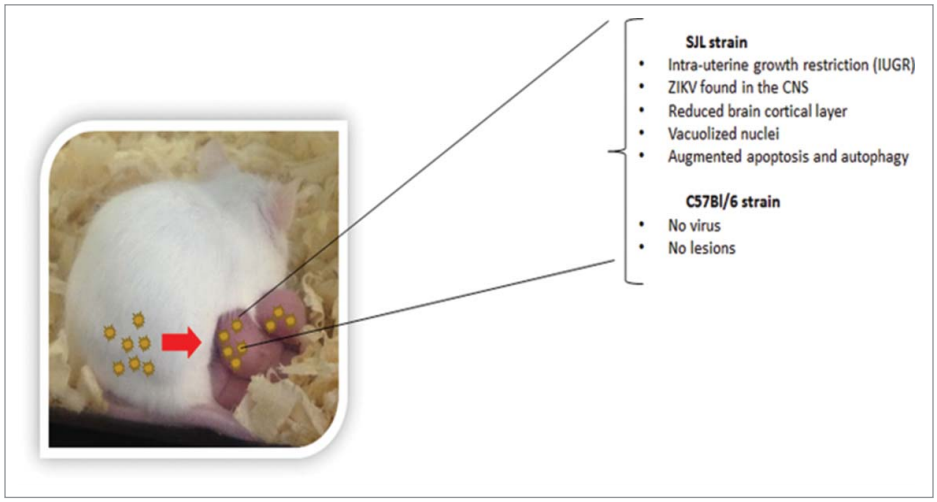

Figure 1. Maternal transfer of Zika to fetus in murine experimental model. Scheme illustrating the placental transference of Zika to fetus in SJL mice that are further born with the highlighted Zika-associated features. C57/Bl6 mice were shown resistant.

layer, with increased caspase-3 staining resulting in significant reduction of the precursor cell markers T-box brain 1^+ and SRY-box 2^+ in neurospheres infected with Zika isolated in Brazil, compared to the well-known MR-766 strain (Uganda). Death of precursor cells resulted in reduction of the cortical thickness in the brains of the pups, with reminiscent vacuolized nuclei with apoptotic and autophagic aspect, which was corroborated by gene expression analysis of brain tissue from pups born from infected mothers.[2] This may indicate that virus circulating in Brazil may somehow have gone through some changes rendering the strain more pathogenic.

In summary, these recent findings greatly add to the understanding of the Zika infection and its relation with microcephaly, and also highlighting its probable teratogenesis, as other findings are being described. Besides, all models established will greatly encourage the studies for vaccine development, as any approach whose goal is to avoid placental transference of the virus and fetal brain destruction must be considered a priority.

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