Transgenic mice are heroes to save us: Novel murine model with conditional expression of the SARS-CoV-2 entry receptor

Russian scientists have created novel COVID-19 murine model with optional and adjustable expression of
hACE2, the main entry receptor for SARS-CoV-2.

BELGOROD, BELGOROD REGION, RUSSIA, April 27, 2021 /EINPresswire.com/ -- COVID-19 is a master killer causing respiratory infection with a high risk of life-threatening complications. Unfortunately, despite the number “-2” in the SARS-CoV-2, scientific and medical communities found themselves quite defenseless against the new coronavirus. Even though the world has already experienced SARS and MERS epidemics, we have just developed vaccines and still do not have effective drugs against SARS-CoV-2 infection. For more than a year laboratories around the world were facing the problem of absence of appropriate animal models to test COVID-19 vaccines and drugs. Moreover, animal models are necessary to shed light on details of disease progression and to reveal a role of different organs and tissues in developing complications.

Actually, there are a raw of SARS-CoV-2 sensitive animals, including nonhuman primates, ferrets, dogs, and cats, but all of them are not routine laboratory species. To solve the problem, transgenic mice expressing human ACE2 have been proposed as an artificial COVID-19 model. In brief, human ACE2 protein is a SARS-CoV-2 entry receptor, and introducing the gene encoding it in the murine genome is the obvious way to “open” murine cells for SARS-CoV-2 invasion. Even several transgenic strains were created long before the first outbreak of COVID-19 just after MERS pandemic in 2007 (McCray et al. 2007; Tseng et al. 2007; Yang et al. 2007). However, these mice were not widely spread in 2020 and some authors proposed novel approaches such as delivery of exogenous human ACE2 gene to the alveolar epithelium via intranasal administration of replication-deficient adenoviruses (Sun et al. 2020; Hassan et al. 2020) or use of genetically modified SARS-CoV-2 with affinity to the own murine ACE2 (Dinnon et al. 2020; Gu et al. 2020).

In May, 2020, Russian scientists from the Institute of Gene Biology and Belgorod State University proposed their own strategy for the creation of a novel COVID-19 murine model. In their strategy there were two pivotal demands for the new line. The first is an ability of spatial and temporal control of SARS-CoV-2 sensitivity by the use of the Cre recombinase system. The second is double humanization meaning to introduce two genes involved in SARS-CoV-2 invasion (ACE2 and TMPRSS2 instead only ACE2). The full description is in the article "On the way from SARS-CoV-sensitive mice to murine COVID-19 model".

In April, 2021, the authors reported successful creation of their own transgenic SARS-CoV-2 sensitive mice. Guided by their initial strategy the scientists created mice with Cre-dependent expression of ACE2 allowing to adjust the localization and the level of transgene expression breeding mice with so called Cre-expressing lines. Cre recombinase is an enzyme that catalyzes the deletion of targeted genomic sequences flanked by LoxP (floxed) sites. In this model a floxed STOP-cassette, sequence disrupting transgene expression, is inserted between the transgene and its promoter. Thus, if Cre recombinase is active in the cell, it excises the STOP-cassette, resulting in the expression of hACE2. In the study Cre line with tamoxifen-dependent Cre-recombinase was used. Such a system requires two-step activation but this is what provides temporal control of transgene expression. Because in these mice Cre-recombinase works only after tamoxifen administration it can be launched on demand in any point of animal lifetime.

The only thing is, instead of double ACE2/TMPRSS2 humanization the hACE2 gene is coexpressed with GFP. The GFP gene encodes Green fluorescent protein, which exhibits bright green fluorescence when exposed to light in the blue to ultraviolet range significantly simplifying the detection of transgenic cells. Thus, in these mice the brighter light tissue has, the more SARS-CoV-2 sensitive it is. For detailed information read the article "Novel transgenic mice with Cre-dependent co-expression of GFP and human ACE2: a safe tool for study of COVID-19 pathogenesis". Right now, these mice serve as a test-system for testing of new Russian vaccines. All obtained results show that mice can be successfully inoculated by SARS-CoV-2 and develop a bright clinical picture.

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