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Cas9-induced immune response: A potential caution for human genome editing

Cheng Cheng Zhang

UT Southwestern Medical Center, United States

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Kang et al. (BBRC 2018) [1] reported that the increasingly common genome editing tool CRISPR (clustered regularly interspaced short palindromic repeats)-Cas9 (CRISPR-associated protein 9) may induce host immune response, based on in *in vitro* results. The authors showed that exogenous Cas9 protein elicited an inflammatory immune response through release of several cytokines in primary human peripheral blood mononuclear cells and a human monocytic cell line. Furthermore, the loss-of-function of the STING-STAT6 pathway blocked Cas9-induced proinflammatory effect, suggesting that interference of the STING-STAT6 axis may decrease the CRISPR-Cas9 system associated immune reaction.

I was the editor for this paper, which was accepted by BBRC on October 13 2018 and e-published on October 20. As a new BBRC editor starting in 2018, I became familiar with the name of BBRC when I became a postdoc at Harvey Lodish's lab in MIT 18 years ago. Young postdocs often enjoyed talking about anecdotes involving former lab members. Through these "gossips", I became aware of the story of Aaron Ciechanover, a former postdoc of Lodish who, as a graduate student, published his seminal discovery about ubiquitin-mediated protein degradation in BBRC. This was a key paper that led to his later winning of a Nobel Prize. I have since kept BBRC uniquely in my mind. After I became a professor at UT Southwestern, my colleague Ilya Bezprozvanny encouraged me to consider an editor position in BBRC, and I said yes immediately.

The implication of the finding of Kang et al. was robust. It echoed prior and later studies that Cas9 may cause immune responses and other potential risks in the host [2–5]. The work also left many questions warranting future investigations, including how Cas9 activates STING-STAT6, why the response is cGAS independent, why in particular three cytokines MIP3α, CD40L, and MPO were significantly induced, what happens *in vivo*, and whether manipulating the STING-STAT6 pathway can reduce the risk of Cas9-induced immune injury in human cells.

Right after the official publication of Kang et al.'s study, researcher Jiankui He's creation of the first human genetically edited babies by CRISPR/Cas9-mediated technology was announced publicly in late November 2018 (https://en.wikipedia.org/wiki/He_Jiankui). This work received worldwide condemnation and has since led to proposals of regulations regarding the manipulation of the human genome using gene-editing techniques. The result of Kang et al.'s BBRC article, along with related studies, could, therefore, potentially contribute to the development plan of future Cas9-related clinical studies. I am excited about the frontline position of BBRC in cutting-edge research that may impact not only research but also the general public and policy-making.

Scientific research has changed a lot in the past 60 years. We will adapt to it and strive to maintain and strengthen the status of BBRC as a leading international journal for fast submission-to-print.

References

[1] R. Kang, S. Zhu, H. Zeh, D. Tang, The STING-STAT6 pathway drives Cas9-induced host response in human monocytes, Biochem. Biophys. Res. Commun. 506 (2018) 278–283.

[2] S.W. Cho, S. Kim, Y. Kim, J. Kweon, H.S. Kim, S. Bae, J.S. Kim, Analysis of off-target effects of CRISPR/Cas-derived RNA-guided endonucleases and nickases,

E-mail address: alec.zhang@utsouthwestern.edu.

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Genome Res. 24 (2014) 132–141.
[3] S. Kim, T. Koo, H.G. Jee, H.Y. Cho, G. Lee, D.G. Lim, H.S. Shin, J.S. Kim, CRISPR RNAs trigger innate immune responses in human cells, Genome Res. 28 (3) (2018) 367–373.
[4] E. Haapaniemi, S. Botla, J. Persson, B. Schmierer, J. Taipale, CRISPR-Cas9 genome editing induces a p53-mediated DNA damage response, Nat. Med. 24 (2018) 927–930.
[5] C.T. Charlesworth, P.S. Deshpande, D.P. Dever, J. Camarena, V.T. Lemgart, M.K. Cromer, C.A. Vakulskas, M.A. Collingwood, L. Zhang, N.M. Bode, M.A. Behlke, B. Dejene, B. Cieniewicz, R. Romano, B.J. Lesch, N. Gomez-Ospina, S. Mantri, M. Pavel-Dinu, K.I. Weinberg, M.H. Porteus, Identification of preexisting adaptive immunity to Cas9 proteins in humans, Nat. Med. 25 (2019) 249–254.