Zhaocai Zhou et al., Virol-mycol 2017, 6:2 (Suppl)
http://dx.doi.org/10.4172/2161-0517-C1-020

Concerted regulation of K48- and K63-linked polyubiquitination of the antiviral sensor RIG-I

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RIG-I is a well-studied sensor of viral RNA that plays a key role in innate immunity. p97 regulates a variety of cellular events such as protein quality control, membrane reassembly, DNA repair, and the cell cycle. Here, we report a new role for p97 with Npl4-Ufd1 as its cofactor in reducing antiviral innate immune responses by facilitating proteasomal degradation of RIG-I. The p97 complex is able to directly bind both non-ubiquitinated RIG-I and the E3 ligase RNF125, promoting K48-linked ubiquitination of RIG-I at residue K181. Viral infection significantly strengthens the interaction between RIG-I and the p97 complex by a conformational change of RIG-I that exposes the CARDs and through K63-linked ubiquitination of these CARDs. Disruption of the p97 complex enhances RIG-I antiviral signaling. Consistently, administration of compounds targeting p97 ATPase activity was shown to inhibit viral replication and protect mice from vesicular stomatitis virus (VSV) infection. Overall, our study uncovered a previously unrecognized role for the p97 complex in protein ubiquitination and revealed the p97 complex as a potential drug target in antiviral therapy.

Biography

Zhaocai Zhou obtained his PhD degree from University of Science and Technology of China, 2004; and received his Post-doctoral training from Brandeis University, and University of Pennsylvania, USA, 2004–2008. He joined the Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences in 2009, and became a Professor of ShanghaiTech University in 2015. His primary research interest is in understanding the signaling mechanism of tumorigenesis and tumor-related immune regulation. His recent work focuses on Hippo/MST signaling pathway and macrophage plasticity.

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