J Antimicrob Chemother. 2014 Oct;69(10):2770-84. doi: 10.1093/jac/dku209. Epub 2014 Jun 20.

Mutations in the chikungunya virus non-structural proteins cause resistance to favipiravir (T-705), a broad-spectrum antiviral.

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Abstract

OBJECTIVES:

T-705, also known as favipiravir, is a small-molecule inhibitor that is currently in clinical development for the treatment of influenza virus infections. This molecule also inhibits the replication of a broad spectrum of other RNA viruses. The objective of this study was to investigate the antiviral effect of favipiravir on chikungunya virus (CHIKV) replication and to contribute to unravelling the molecular mechanism of action against this virus.

METHODS:

The anti-CHIKV effect of favipiravir was examined in cell culture and in a mouse model of lethal infection. A five-step protocol was used to select for CHIKV variants with reduced susceptibility to favipiravir. The resistant phenotype was confirmed in cell culture and the whole genome was sequenced. The identified mutations were reverse-engineered into an infectious clone to confirm their impact on the antiviral efficacy of favipiravir.

RESULTS:

Favipiravir inhibits the replication of laboratory strains and clinical isolates of CHIKV, as well as of a panel of other alphaviruses. Several favipiravir-resistant CHIKV variants were independently selected and all of them in particular acquired the unique K291R mutation in the RNA-dependent RNA polymerase (RdRp). Reverse-engineering of this K291R mutation into an infectious clone of CHIKV confirmed the link between the mutant genotype and the resistant phenotype. Interestingly, this particular lysine is also highly conserved in the RdRp of positive-stranded RNA viruses in general.

CONCLUSIONS:

This study provides an important insight into the precise molecular mechanism by which favipiravir exerts its antiviral activity against (alpha)viruses, which may be of help in designing other potent broad-spectrum antivirals.

KEYWORDS:

alphavirus; nsP4; polymerase