Screening of kinase inhibitor library revealing lead compounds for treatment of cystic echinococcosis

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Aims: The metacestode stage of two *Echinococcus species*, E. granulosus sensu lato and E. multilocularis cause cystic echinococcosis (CE) and alveolar echinococcosis (AE), respectively. These diseases remarkably impact on the health of population. Although surgical removal of cyst is the cure treatment, about 90% of patients with echinococcal infection are treated by albendazole. However, as the drug is not parasiticidal, the patients with AE or CE have to take the drug for a long time, even for the whole life. The treatment of these diseases urgently need an effective drug.

Material and Methods: In the study, by using *in vitro* cultivation of E. granulosus protoscoleces and micro-cysts, we primarily screened 378 kinase inhibitors at 5 μM, which revealed 51 compounds showing killing efficacy. Further using 1 μM, 7 compounds were keeping killing efficacy *in vitro*. Dose-response assays revealed that 2 of the compounds, S2243 and S2895, had LC50 value below 2.5 μM. We then incubated cysts of E. granulosus collected from infected mice with S2895 and S2243 at 20 μg/L, which resulted in 60% of the cysts dead in 24 h. For *in vivo* efficacy trial, BALB/c mice were transferred with 50 micro-cysts and after 3 month postinfection, each of the mice was orally given these two drugs a dose of 15 mg/kg of body weight for one month. An increase in cyst mortality rate was observed compared to that of those collected from control mice.

Conclusions: Our study identifies that the two kinase inhibitors showed parasiticidal in both *in vitro* and *in vivo*, indicating these two inhibitor may be the lead-compounds for drug development against echinococcosis.

Recent Publications:

1. Jianling Bao,Jun Li(2018) Donald McManus. Echinococcus granulosus infection results in an increase in Eisenbergiella and Parabacteroides genera in the gut of mice, Frontiers in Microbiology.29 November 2018.
2. Hui Wang, Jun Li (2018) Echinococcus granulosus sensu stricto: silencing of thioredoxin 4 peroxidase impairs the differentiation of protoscoleces into 5 metacestodes. Parasite 25, 57.
3. Zhuang-Zhi Zhang,Wen-Bao Zhang(2018)Dog vaccination with EgM proteins against Echinococcus granulosus.[J]. Infectious Diseases of Poverty,7(1):61.
4. Mei Yang, Wenbao Zhang(2017)Cloning and characterization of an Echinococcus granulosus ecdysteroid hormone nuclear receptor HR3-like gene.[J]. Parasite-journal De La Societe Francaise De Parasitologie, 24:36
5. Weisi Wang, Jun Li(2017)In vitro and in vivo efficacies of novel carbazole aminoalcohols in the treatment of cystic echinococcosis. J Antimicrob Chemother. Jul 24. doi: 10.1093/jac/dkx250.
6. Wu C, Li J(2017)Genetic variation of mitochondrial genes among Echinococcus multilocularis isolates collected in western China. Parasit Vectors. May 30;10(1):265. doi: 10.1186/s13071-017-2172-y.
7. Wang H, Li J (2016) In vitro culture of Echinococcus multilocularis producing protoscoleces and mouse infection with the cultured vesicles. Parasites & Vectors.Jul 25;9(1):411

Biography

Jun Li is a professor of Xinjiang Medical University and a senior research fellow of State Key Laboratory of Pathogenesis, Prevention and Treatment of High Incidence Diseases in Central Asia, Xinjiang Medical University, Urumqi, China. He received her B. Sc from Xinjiang Medical University. In 2004, she obtained her PhD at the University of Queensland working on developing diagnosis tool for detecting cystic echinococcosis. She then spent 3 years working on PanBio for developing diagnosis kit for infectious diseases. From 2008-2013, she worked on molecular biology of Echinococcus as a senior research officer in Molecular Parasitology Laboratory, Infectious Diseases Division, QIMR Berghofer Medical Research Institute, Brisbane, QLD, Australia. She has published more than 30 papers/articles in the international journals in her research career.