

'Virological penicillin': Plant MIR2911 directly targets influenza A viruses

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In a new study, Chen-Yu Zhang's group at Nanjing University present an extremely novel finding that a plant microRNA, MIR2911, which is enriched in honeysuckle, directly targets influenza A viruses (IAV) including H1N1, H5N1 and H7N9. Drinking of honeysuckle soup can prevent IAV infection and reduce H5N1-induced mice death.

MicroRNAs (miRNAs) are a class of 19-24 nucleotide non-coding RNAs that do not encode for proteins. MiRNAs bind to target messenger RNAs to inhibit protein translation. In previous studies, the same group has demonstrated that stable miRNAs in mammalian serum and plasma are actively secreted from tissues and cells and can serve as a novel class of biomarkers for disease and act as signaling molecules in intercellular communication. They have also reported that plant miRNAs can enter into the host blood and tissues via the route of food-intake. More importantly, once inside the host, the food-derived exogenous miRNAs can regulate host physiology by regulating host "target" genes.

Here, they report a surprising finding that MIR2911 from a Chinese herb honeysuckle can suppress IAV infection. Firstly, MIR2911 was found to be selectively retained in the boiled decoction of honeysuckle, and to be delivered into mouse plasma and lung tissue after drinking honeysuckle decoction. Then, the authors showed that MIR2911 represses various influenza viruses by targeting PB2 and NS1, two genes that are known to be required for influenza viral replication. Moreover, both synthetic MIR2911 and endogenous MIR2911 in honeysuckle decoction showed effective protection of animals from H1N1 infection,

while such protection is dependent on the MIR2911-binding sites in the PB2 or NS1 genes. Last, MIR2911 is also effective to suppress the replication of influenza viruses H5N1 and H7N9, indicating a broad-spectrum anti-IAV effect of MIR2911.

This work is important for the following reasons:

- It identifies MIR2911 as the first, active component directly targeting influenza A virus (IAVs). It is well known that Spanish Flu (H1N1) caused about 50 million people death. Recently reported mortality cases of pathogenic IAVs, such as H5N1 and H7N9 highlight the threat that these viruses pose to public health. Due to the rapid mutation and evolution of IAVs, it is almost impossible to prevent or cure the IAV infection by the same treatment. It is thus urgently to explore novel therapeutic strategy. With this in mind, plant MIR2911 is an ideal reagent for suppressing IAV infection, and it is fully expected that MIR2911, as well as MIR2911-enriched honeysuckle decoction, will be widely used for treatment of IAVs infection.
- It is the first demonstration that a natural product can directly target virus. Since Fleming discovered penicillin nearly a century ago, antibiotics have been developed to target various bacterial infections and have saved the lives of millions of people. Unfortunately, no natural product that is effective against viral infection has been identified so far. As the first natural product directly targeting different IAVs, plant MIR2911 not only is the first active component identified in Traditional Chinese Medicine that directly targets various IAVs, but also may represent a novel type of natural product that effectively and directly suppresses viral infection. Furthermore, one of their ongoing studies shows that MIR2911 also directly targets Ebola virus, which is pandemic in West Africa and is becoming a crisis of public health. Thus, MIR2911 is able to serve as the

"virological penicillin" to directly target various viruses.

- Physiological concentration of MIR2911 in honeysuckle decoction sufficiently targets IAVs. For thousand years, Chinese have been drinking honeysuckle (also termed *Lonicera japonica*) decoction to treat influenza [viral infections](#) and the results show that honeysuckle decoction has a broad-spectrum anti-viral activity. It makes much easier and simpler to clinical usage by drinking honeysuckle tea/decoction. These results also provide another evidence to prove their previous discovery that dietary exogenous miRNAs are able to be functionally absorbed by mammalian gastrointestinal tract and play an important regulatory role in a cross-kingdom manner.
- It further supports that exogenous small RNA via the route of food-intake can be delivered into host tissues with sufficient functional concentration. Peak level of MIR2911 in mouse lungs after administration honeysuckle soup is 2.6×10^{-5} fmol (equivalent to 15600 copies) per 100 pg of total RNA. Given that about 70 μ g total RNA can be extracted from 35 mg mouse lung tissues, and each mouse lung weighs approximate 0.12 g and contains 110-120 million cells, MIR2911 is estimated about 300~400 copies per cell. Another quantification approach by normalizing to U6 snRNA reveals that copy number of MIR2911 is even higher. Previous report has shown there are in average 400,000 copies of U6 snRNA per cell. Peak level of MIR2911 is about 250-fold less than U6 snRNA. Thus, there are about 1600 copies of MIR2911 in each lung cell. The quantification of MIR2911 is consistent with their previous study that MIR168a were present in mouse liver at approximate 800 copies per cell after feeding mice with fresh rice.

More information: Zhou et al.: " Honeysuckle-encoded atypical microRNA2911 directly targets influenza A viruses " Publishing on Cell Research, October 7, 2014.

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