Repurposing staples for viruses: applying peptide design to RSV prophylaxis

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Respiratory syncytial virus (RSV) is responsible for lower respiratory tract infections and annually results in 200,000 deaths worldwide. Despite the burden of RSV-associated disease, treatments and preventative measures are limited. In this issue of JCI, Bird and colleagues describe their work using a peptide stapling technique that allowed synthesis of a stable peptide mimic of a portion of the RSV fusion protein. Pretreatment of cells with the stable peptide effectively blocked virus entry. When introduced into mice prior to RSV exposure, the peptide produced a substantial prophylactic effect. This work provides a new way forward in RSV prevention.

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Viral infection prophylaxis: are peptides back on the table?

The question of efficacy for antiviral peptides often comes down to the issues of stability and delivery. Will the peptide assume the required conformation and resist degradation once introduced into an infected host, and will it reach the site of infection? In answer to these pharmacological questions, Bird et al. showed that their stapled peptides display a marked antiviral effect when administered to mice prior to RSV infection (11). By instilling SAH-RSVF intranasally, a peptide barrier is effectively created at the RSV entry point. Infection in the nares was markedly reduced by pretreatment with SAH-RSVF, which indicates that the peptides are stable and functionally active. Perhaps more impressive was the observation that peptide activity was not limited to the site of administration. RSV spread to the lower respiratory tract and caused substantial lower respiratory disease, but during the course of their experiments, the authors found that the intranasally administered peptide also markedly decreased pulmonary RSV infection (11). Incorporation of the hydrocarbon staples appears to have stabilized SAH-RSVF to the point that it can travel to a distant site of infection without compromising its biological potency.

The initial route of administration, however, sidesteps the question of how to effectively deliver a peptide to a systemic site of infection. RSV has the “advantage” of being a respiratory tract virus for which the route of entry is a convenient site for peptide administration. For viruses with alternative routes of entry or for persons already infected, administration at the entry site may not be effective. To circumvent this problem, Bird et al. turned to nanotechnology to further augment their antiviral treatment, generating a chitosan-based nanoparticle to encapsulate SAH-RSVF with the goal of improving efficacy and delivery (11). This technique has been shown to be effective with both small-molecule and nucleic acid–based treatments (15, 16). The nanoparticle-encased peptides were administered intratracheally, delivering the SAH-RSVF peptides directly to the site of pulmonary RSV infection, rather than just at the point of entry. Peptide incorporation into the nanoparticle increased the extent and uniformity of delivery, which led to a striking improvement in viral prophylaxis over peptide alone (11).

Conclusions and future directions

In today’s multidisciplinary research environment, the traditional divisions among the basic sciences have become blurred, providing exciting opportunities to combine different approaches, improving old techniques for disease therapeutics and developing new ones. The study by Bird...
et al. (11) is an excellent example of scientists pushing past the traditional limits of their discipline to take advantage of biology, chemistry, and nanotechnology and overcome the shortcomings of clinical applications of antiviral peptides. While the authors focused on the use of stabilized peptides and nanoparticle delivery as prophylactic measures, their cell-based work demonstrating robust inhibition of RSV fusion and entry (11) suggests that the peptides could be adapted as antiviral therapeutics for persons with RSV infection. Moreover, the formation of hairpin-linked 6-HBs is a classic hallmark of many fusogenic enveloped viruses, including Ebola virus, HIV, and SARS coronavirus, which all bring viral and cellular membranes together via formation of a 6-HB in the same fashion as RSV (17). It is possible that the present findings made with RSV could be adapted to combat a host of pathogenic human viruses, both as prophylactic agents and as antiviral treatments.

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Three years ago, two research groups independently identified a previously undescribed T cell cosignaling molecule; one referred to it as V-domain Ig suppressor of T cell activation (VISTA), and the other used the term programmed death-1 homolog (PD-1H). Recombinant and ectopically expressed PD-1H functions as a coinhibitory ligand for T cell responses. However, the function of endogenous PD-1H is not clear. In this issue of the JCI, Flies and colleagues demonstrate that endogenous PD-1H on both T cells and APCs serves as a coinhibitory molecule for T cell activation and provide further support for targeting PD-1H as a therapeutic strategy for transplantation and cancers.

Life is never dull, especially if you are interested in T cell cosignaling molecules. The identification of new members of this family can lead not only to new paradigms in immune recognition, but can also affect the treatment of cancer and autoimmune diseases (1–4). Among the newest additions to the T cell cosignaling family is an immunoglobulin superfamily member that bears two different names due to its independent discoveries three years ago: V-domain Ig suppressor of T cell activation (VISTA) and programmed death-1 homolog (PD-1H).

Wang et al. named this molecule VISTA (5), based on significant sequence homology with B7 homologue 1 (B7H1) and the ability of recombinant VISTA-Fc protein and ectopic expression of VISTA on APCs or tumor cells to inhibit T cell proliferation. In an independent study, Flies and colleagues identified the same molecule and named it PD-1H due to greater overall sequence and gene structure similarities with programmed death-1 (PD-1) (6).

Same target, different results

Remarkably, the antibodies produced against the molecule by Wang and colleagues and Flies et al. had starkly different effects. Whereas Wang et al. found that their anti-VISTA antibody exacerbated EAE, Flies et al. found that their anti-PD-1H antibody suppressed graft-versus-host diseases (GVHD) to such an extent that fully allogeneic bone marrow chimera mice (BALB/c to lethally irradiated C57BL/6 mice) could be obtained following a single dose of anti-PD-1H antibody.