Influenza - Time to Target the Host?

CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Influenza — Time to Target the Host?

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Influenza A viruses make formidable combatants. Their ubiquity and diversity in nature, coupled with a rapid capacity to evolve, render them one of the most mutable pathogens faced by humanity. The avian influenza A (H7N9) outbreak in China, which shows many troubling features, would be a timely reminder of the threat, if any were needed.

Vaccines and antiviral drugs are available to prevent and treat infection, but both are rendered less effective by the variability of the virus. In particular, our ability to intervene using specific therapies in critically ill patients with severe influenza infection is limited, with the current antiviral agents showing disappointing results even in the absence of obvious viral resistance.[1]

In contrast to the virus, humans do not change quickly. It is therefore an enticing strategy to try to overpower influenza not by targeting the virus itself but rather by finding ways to make our own cells less permissive to viral replication. Such a strategy may limit the ability of the virus to evolve resistance.

Morita et al. therefore set out to identify human lipid products that restrict influenza replication in vitro.[2] Unlike models in many other diseases, cell-culture models in influenza infection have direct conceptual relevance to clinical practice: if we can find ways to make cells in a petri dish less supportive of viral replication, it follows that the same treatments may restrict viral replication in a whole organism.

The investigators screened libraries of bioactive lipids, including prostaglandins, leukotrienes, and numerous other mediators, to find compounds that restricted influenza replication in a human cell line (Fig. 1). Notably, all these lipids are endogenous mediators produced by host cells, derived from endogenous lipids. One such mediator produced when n–3 polyunsaturated fatty acids (fish oils) are available is protectin D1. This turned out to be the most potent inhibitor of viral replication; it appears to work by inhibiting the nuclear export of viral mRNA.

When Morita et al. characterized lipid mediators in the whole organism, using mass spectroscopy to quantify lipid species (lipidomics) in a mouse model of severe influenza infection, they found that the protective mediator protectin D1 was down-regulated in the lungs of infected animals.

The authors then administered protectin D1 intravenously to mice before infecting them intratracheally with influenza virus and found that the compound was protective against influenza. So far so good, and the magnitude of the effect was impressive, given the generally modest effects of protectin D1 on virus replication in cell culture.

However, a major roadblock in translational research is the ability to find interventions that are active at a clinically relevant time point. Patients do not usually present early in disease progression; in many cases, substantial organ failure has ensued before patients with severe influenza infection present to any medical services. For this reason, it is highly important that protectin D1 was effective in altering the course of disease in mice, even when treatment was initiated 2 days after infection with influenza virus. When protectin D1 was administered in combination with the antiviral agent peramivir, there was an impressive reduction in mortality. Without treatment, all the mice died. With treatment, they all survived. With peramivir treatment alone, approximately 35% of the mice survived.

Does protectin D1 have the potential to become a new therapy for influenza infection? Perhaps. It has some advantages over other compounds as it sets out on the long road to-

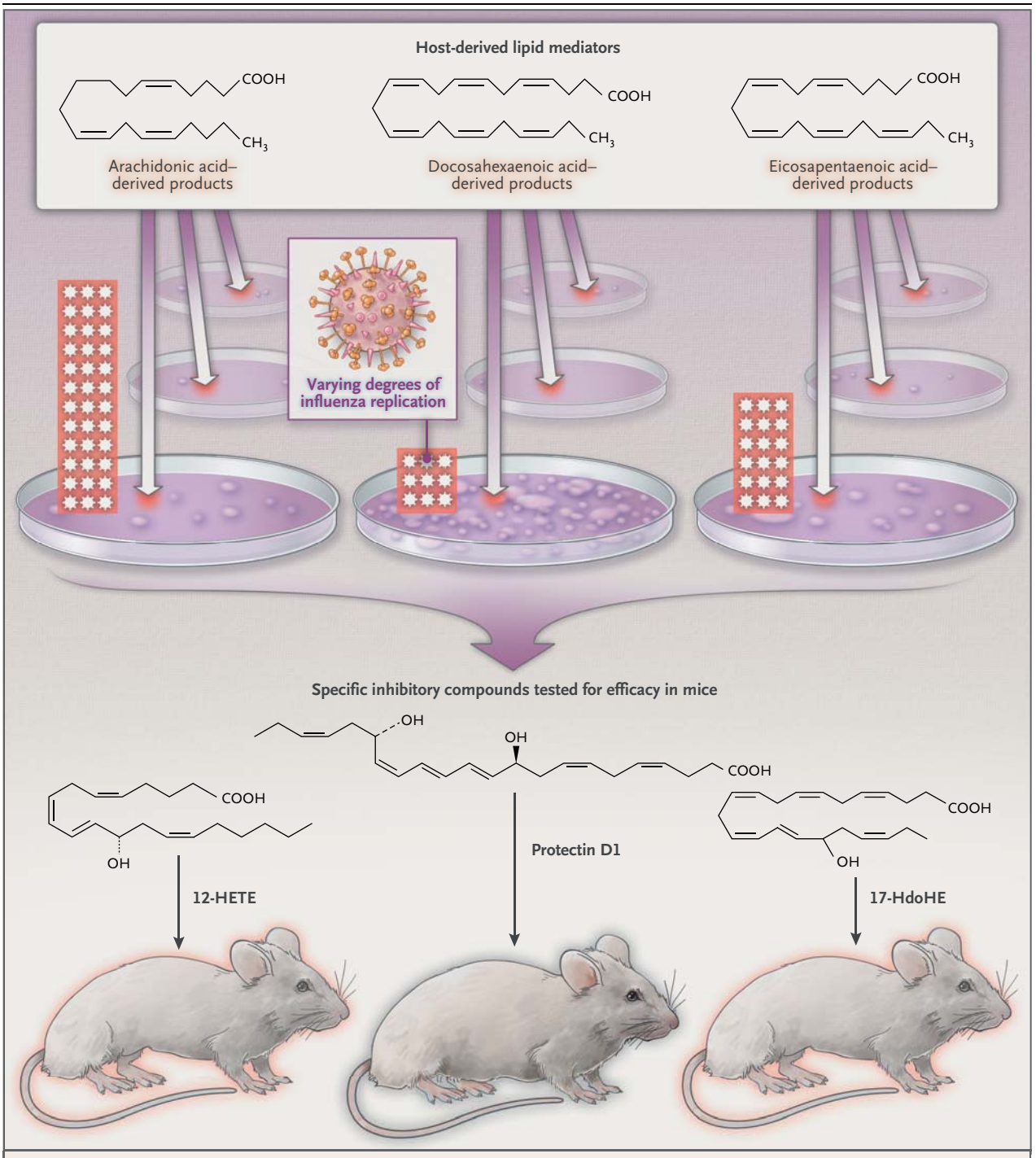

Figure 1. Identification of Protectin D1 as a Potential Therapeutic Agent.

In the discovery process used to identify protectin D1 as a potential therapeutic agent to modulate the host response in severe influenza infection, a wide range of different host lipid mediators were tested in cell-culture models of viral replication. Candidate mediators that restricted replication in vitro were then tested in mouse models of severe disease. With protectin D1, mice had significantly reduced mortality, whereas mice treated with 12-hydroxyeicosatetraenoic acid (12-HETE) or 17-hydroxydocosahexaenoic acid (17-HdoHE) had severe illness and high mortality, similar to infected animals left untreated.

ward clinical practice. It is an endogenous mediator and appears to be potently active, albeit in combination with another drug, in a mammalian model. However, some common limitations of lipid mediators, including poor oral bioavailability, short half-life, and potential toxicity,[3] are also likely to apply and may restrict initial drug-development efforts to the intensive care unit. Nevertheless, the potential of this compound in critical illness may extend beyond influenza infection — evidence exists for potentially beneficial effects in animal models of other life-threatening conditions, including peritonitis, asthma, and acute kidney injury.[4] Another possibility is that host variation in the key protectin D1 pathways, such as the enzyme 12/15 lipoxygenase, may explain some of the variation in individual susceptibility.[5]

As with all therapies in the first stage of development, the odds are stacked against protectin D1. If it fails, perhaps the most lasting effect of this work will be the successful demonstration of the principle that screening for host lipid factors that restrict replication can result in viable therapeutic candidates.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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1. Hsu J, Santesso N, Mustafa R, et al. Antivirals for treatment of influenza: a systematic review and meta-analysis of observational studies. Ann Intern Med 2012;156:512-24.
2. Morita M, Kuba K, Ichikawa A, et al. The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. Cell 2013;153:112-25.
3. Porter CJ, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: optimizing the oral delivery of lipophilic drugs. Nat Rev Drug Discov 2007;6:231-48.
4. Serhan CN, Chiang N, Van Dyke TE. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. Nat Rev Immunol 2008;8:349-61.
5. Horby P, Nguyen NY, Dunstan SJ, Baillie JK. The role of host genetics in susceptibility to influenza: a systematic review. PLoS One 2012;7(3):e33180.

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