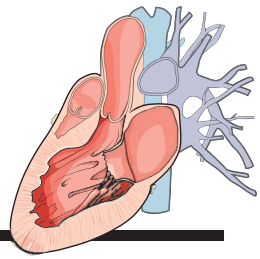
INSIGHTS

Targeting mutated myosin *p. 556* ▸

An all-antiferromagnetic magnetic memory *p. 558*



No larger than a pinhead in size, a female *V. destructor* uses a worker bee as transport and food source.

PERSPECTIVES

ECOLOGY

The mite that jumped, the bee that traveled, the disease that followed

Global expansion and trade contributed to the declining health of honeybees

By **Ethel M. Villalobos**

European honeybees are among the best-studied and most widely recognized insect species in the world. Originally kept for honey production, they have become the flagship species for pollination and large-scale agriculture. Since large colony losses were reported across the United States in 2006, researchers have investigated the myriad factors that contribute to the decline in honeybee populations. In particular, the aptly named *Varroa destructor* mite (see the photo) and the deformed wing virus (DWV) have been clearly linked to colony collapse (*1*). On page 594 of this issue, Wilfert *et al.* use a phylogeographic analysis to examine the evolutionary origin and mechanisms for the global spread of the DWV (*2*).

Based on molecular data from 17 countries and 32 geographical regions, the authors confirm that DWV is an endemic

PHOTO: MATT BERTONE

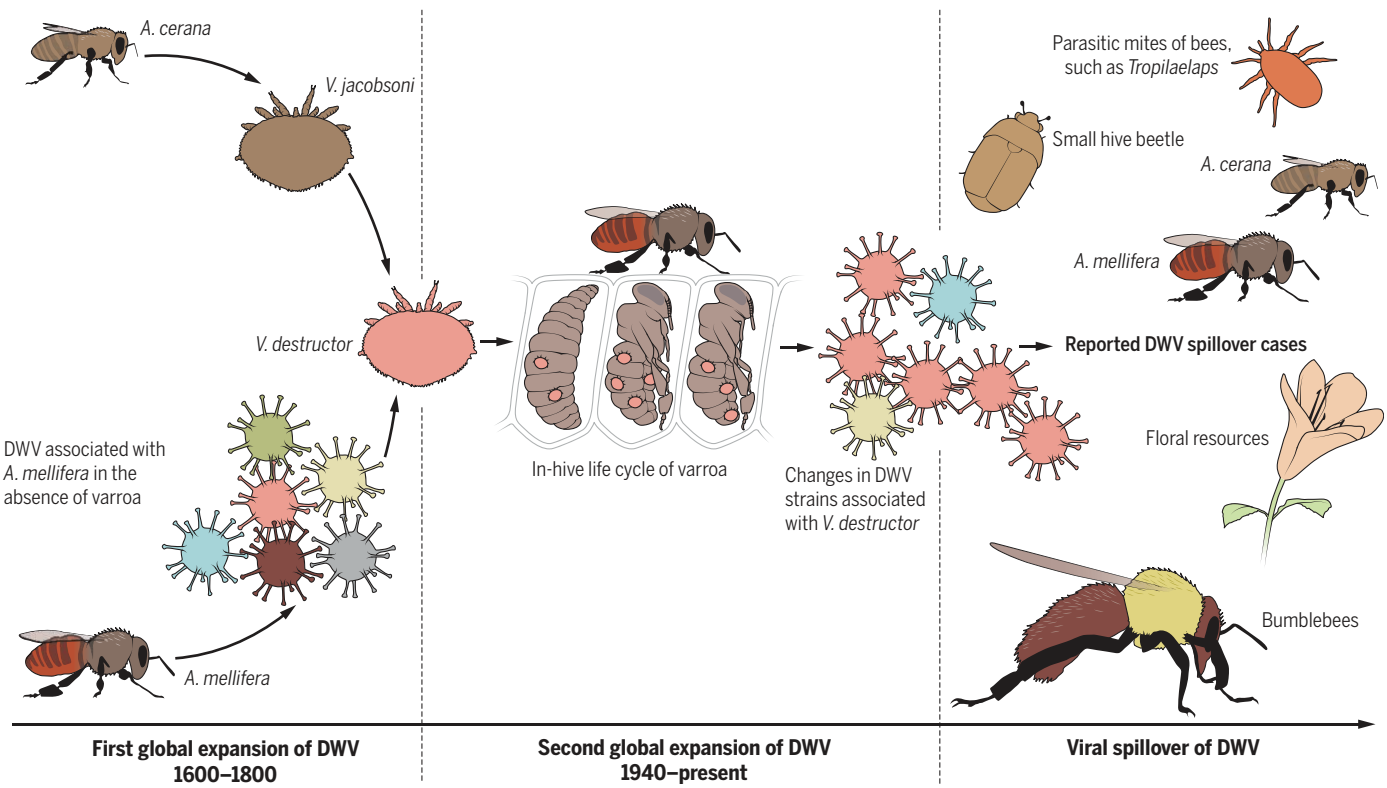
pathogen of the European honeybee, *Apis mellifera* (see the figure). Thus, the recent honeybee decline associated with DWV constitutes the reemergence of a previously existing disease of *A. mellifera*. This reemergence was facilitated by the spread of the new vector *V. destructor* and by human transport of honeybee colonies from Europe and North America to other geographical regions.

The DWV epidemic is part of a global trend of disease reemergence affecting a diverse range of organisms. In the past 20 years, an increase in viral diseases of vegetable crops has greatly affected productivity worldwide. This change was driven by the spread of an insect vector, the whitefly, *Bemisia tabaci*, and the human transport of infected plants (*3*). In the case of the European honeybee and *V. destructor*, natural genetic variation in the brood parasite *Varroa jacobsoni* facilitated its jump from the Asian honeybee (*Apis cerana)* to the European honeybee (*A. mellifera*). Two haplotypes derived from *V. jacobsoni* have adapted to reproduction on *A. mellifera*; both of these haplotypes are now grouped under *V. destructor* (*4*). This novel vector-host relationship was mediated by human introduction of European honeybees to central and southeastern Asia, bringing these two closely related bee species (*5*) into contact.

Martin *et al.* (*1*) have shown that the arrival of *V. destructor* on previously varroa-free islands in Hawaii led to a rapid reduction in DWV strain diversity, coupled with a dramatic increase in virulence. Wilfert *et al.* (*2*) now track the historical global movements of DWV and show that in the recent past, the virus has spread to multiple hosts. Cross-species infections and viral reemergence are more likely to occur if the virus is a "generalist" that can recognize a range of cell receptors and invade a diversity of tissues and hosts (*6*, *7*). According to Wilfert *et al.* (*2*), three viral fragments of the DWV (*rdrp*, *vp3*, and *lp*) show little host specificity, a trait that would favor global expansion. The data provide solid evidence for transmission of DWV from the ancestral host, *A. mellifera*, to *V. destructor,* as well as to novel hosts, such as *Tropilaelaps clarea* (another Asian honeybee mite) and bumblebees.

As with the viral-whitefly association (*3*), the role of humans in the global spread of the European honeybee, the varroa mite, and DWV is undeniable. The first expansion of the honeybee's range began in the early 1600s and continued until the late 1800s. Honeybee colonies were transported on slow-moving cargo ships, packed in iceboxes to simulate winter months and slow their metabolism (*8*). The second large wave of expansion occurred in the past 75 years, promoted by the development of large-scale modern agriculture (see the figure). Wilfert *et al.* use 20th-century samples to reconstruct the origin and migration rates of the DWV during this second wave and correlate the virus expansion with global patterns of mite distribution. Europe and North America are clearly the main centers for transmission of DWV to other areas of the world. Varroa-free areas, such as Australia and some islands in Hawaii, show weaker migration rates of DWV due to geographical isolation, reduced trade, and restrictions on the import of live honeybees to these regions.

Knowledge of the history and ecology of new diseases provides a framework in which to understand the origins, effect, and possible strategies for pathogen control.



Global spread. As shown by Wilfert *et al*., factors driving the global reemergence of DWV, an endemic pathogen of the European honeybee, include human-mediated movement of managed bees, adaptation of a vector mite to a novel host, and changes in the viral population. The first global movement involved managed bees without the vectoring mite. The second, more recent, event occurred after the varroa mite had come into contact with DWV. The increased viral levels and pathogenicity of DWV in the presence of *V. destructor* appear to be linked to a viral spillover to floral resources and a number of arthropod species, including native solitary and social bees.

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ILLUSTRATION: P. HUEY/*SCIENCE*

Wilfred *et al.* provide such a tool by combining molecular data, geography, and a time line for the global dispersion of DWV and *V. destructor*. The high levels of DWV due to mite-related transmission (*9*) affect not only honeybees, but also possibly other insects that may come into contact with the virus (*10*) and food resources they share (*10*, *11*). DWV has been detected in various insect groups that play dramatically different ecological roles, including insect predators and scavengers, pollinators, and pest species that live inside the colony (*10*).

The increased prevalence of DWV in infected colonies, combined with the high density of colonies in certain regions, creates a favorable environment for the virus to spread. The global snapshot provided by Wilfert *et al.* suggests that certain geographic areas have unique ecological conditions that may shed light on the evolution of the DWV and the host-vector relationship. South America, for example, hosts a hybrid of the European and the African honeybee, *Apis scutellata*, which shows genetic differences in immune responses and a greater tendency to remove brood infected by varroa from the hive (*5*). The overlapping ranges of *A. mellifera* and *A. cerana* in Southeast Asia provide an opportunity to compare noncoding RNAs that may be related to antiviral activity (*12*).

Finally, three master variants of DWV—type A, type B, and the newly discovered master variant type C—may produce recombinants, compete with each other within the host colony, and differ in virulence levels (*7*). The few remaining varroa-free refugia provide a unique opportunity to study the numerous master strains that exist without the vector's input. In-depth studies of virus, vector, and host populations in diverse geographical regions will help to understand how viruses spread to new hosts and adapt to new environments. ■

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HEART DISEASE

Throttling back the heart's molecular motor

A small molecule inhibits mutated forms of myosin that cause cardiac hypertrophy

By **David M. Warshaw**

A young athlete collapses and dies during competition. Autopsy reveals an enlarged heart with thickened walls in which the cardiac muscle cells are in disarray and surrounded by fibrotic tissue. Until 1990, the cause of such sudden death was unknown. This devastating condition, called familial hypertrophic cardiomyopathy (HCM), was eventually linked to a mutation in myosin (*1*), the heart's molecular motor. Today, more than 300 separate HCM-causing mutations have been identified throughout the myosin molecule. On page 617 of this issue, Green *et al.* (*2*) describe a small molecule that binds to myosin and inhibits its activity, delaying the onset and progression of the disease in a mouse model. The study offers hope that a "simple" remedy for HCM may be possible.

Myosin is an adenosine triphosphatase (ATPase) enzyme that cyclically interacts with cytoskeletal actin filaments to convert chemical energy—through its hydrolysis of ATP—into force and motion that powers the heart's pumping action. Muscle cells of the heart shorten by the sliding of actin filaments past myosin filaments in the sarcomere, the cell's smallest contractile unit. Each myosin filament is composed of ~300 myosin molecular motors that generate power through their interaction with actin (see the figure). Mutation in the human β-cardiac myosin gene (*MYH7*) results in the amino acid substitution of arginine at position 403 with glutamine (R403Q) in the molecular motor. With 50% of R403Q patients dying by age 35 (*3*), understanding the molecular basis of the mutation's primary insult to the myosin motor's power-generating capacity has been a matter of vigorous debate.

> ***"...a 'simple' remedy for HCM may be possible."***

Initially, it was proposed that a loss in myosin power output was the causative factor of HCM, and that remodeling of the heart was a failed compensatory response (*4*, *5*). To address this question, a mouse model of HCM was generated in which the animal develops a hypertrophied heart and dies suddenly when physically challenged—outcomes resulting from a single R403Q allele, as occurs in humans (*6*). Mice homozygous for R403Q die within 7 days of birth, emphasizing the devastating impact of this mutation (*6*). Analysis of pure mutant α-cardiac myosin (which is 92% identical in its wild-type primary sequence to human β-cardiac myosin) isolated from the hearts of these mutant mice revealed that the motor protein had twice the force- and motion-generating capacity compared to normal myosin (in a simplified in vitro model of cardiac contraction), and also had equally enhanced ATPase activity (*7*). These characteristics raise the potential for excessive ATP utilization and, consequently, boost energy demand, which could signal hypertrophic remodeling (*8*). These gains of function for the mutant form of myosin should not have been surprising, given that clinical measures of cardiac performance describe the HCM heart as hyperdynamic (*9*). Many of the mutations discovered in myosin's motor domain have a tendency toward enhanced mechanical and/or ATPase capacities (*10*)—specifically, the R403Q, R453C, and R719W mutations studied by Green *et al.*, in which arginine (R) at position 403, 453, and 719 is substituted with glutamine (Q), cysteine (C), and trypophan (W), respectively.

In some patients with HCM, surgical thinning of the septal wall between the right and left ventricle can reduce the thickened wall's encroachment on the left ventricle's outflow tract (*11*); for severe cases, cardiac transplantation may be the only option. With 1 in 500 individuals having HCM, a far less invasive intervention is desirable. Green *et al.* tested the hypothesis that if HCM mutations lead to enhanced myosin power production, then early intervention using small-molecule inhibitors of myosin power generation should prevent hypertrophy. MyoKardia, a company founded by four authors of the Green *et al.* study, developed such a small-molecule in-

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