to the inhibitor having a secondary ability to induce apoptosis in uninfected cells.

One of the interesting findings reported by the authors is that after the onset of infection, a particular type of lung cell called a type I alveolar epithelial cell contained around 80-fold more viral RNA than did any other type of lung cell. This fits with previous observations that destruction of this particular cell type, beginning at a threshold of destruction of 10% of these cells, is correlated with loss of lung function and lethality[6]. Consistent with the effects of UH15-38 and the potential importance for disease treatment using UH15-38, these cells express all of the required necroptotic machinery and, on infection, MLKL becomes phosphorylated, a process that can be blocked by UH15-38. By contrast, activation of caspase-8 and caspase-3 is unaffected by UH15-38.

The most striking finding presented by the authors is that UH15-38 works for at least 5 days post-infection. In earlier studies in mice, antivirals approved for use in the clinic, such as oseltamivir and zanamivir, worked best when delivered before infection (prophylactically) and did not provide notable protection if delivered 48 hours after infection commenced[7,8]. These drugs are therefore usually recommended only for at-risk patients within 48 hours of the first signs of symptoms. It would be interesting if the two types of inhibitor were tested head-to-head to determine whether the superiority of UH15-38 can be confirmed and whether the findings have relevance for clinical treatments.

Is UH15-38 particularly effective in influenza because it accumulates in the lung or because the lung is particularly susceptible to necroptosis? Both are possible. Gautam and colleagues report that the level of UH15-38 in the lung is eightfold higher than the level in blood plasma. There have been a number of reports regarding other lung conditions, including chronic obstructive pulmonary disease and asthma, in which necroptosis has been shown, at least in mouse models, to contribute to disease severity[9]. Conversely, a paper examining the role of necroptosis in SARS-CoV-2 infection, on the basis of studies of lethal infections in mice lacking MLKL, indicates that necroptosis has no role in disease severity[10], suggesting that inhibiting necroptosis will not be a panacea for all respiratory diseases.

Using this new RIPK3 inhibitor to tackle influenza infections therefore strikes a balance, reducing the force of the inflammatory response but sustaining its antiviral effect. We eagerly await clinical trials that could help with the next pandemic.

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Biomechanics

The insect-wing hinge comes into focus

Tanvi Deora

The hinge enables insects to control their wing movements, but how it works is hard to study. Multidisciplinary research, using imaging and machine-learning methods, now sheds light on the mechanism that underlies its operation. **See p.795**

Winged insects, including butterflies, wasps and beetles, are some of the most successful animals on the planet, in terms of numbers of species and of individuals. Part of this success comes from their ability to fly and from the evolution of wings, which have evolved as a new type of appendage, independently of limbs. The wing is connected to the insect body through an exquisite hinge. Although the wing hinge is an important joint, its small size, its fast movement and researchers' inability to directly observe it have made understanding how it works difficult. On page 795, Melis *et al.*[1] go a long way to solving this riddle.

Insects such as flies and bees flap their wings hundreds of times a second to perform extremely rapid, yet controlled, flight manoeuvres. These animals have evolved specialized muscles and body appendages that enable such high-frequency wing movements[2]. Wing motion is powered by a set of muscles called the indirect flight muscles, which do not attach directly to the wings, but instead attach to and deform the insect's exterior surface — its exoskeleton. These deformations are transmitted to the wing by the hinge, a complex joint that consists of a series of tiny, hardened structures known as sclerites (Fig. 1). Each sclerite transmits force to its neighbour — in a way reminiscent of a series of gears — thereby transforming tiny exoskeletal deformations into large back-and-forth wing movements.

Small steering muscles, also called direct flight muscles, attach to sclerites and apply force directly to them to fine-tune the wing movements on a stroke-by-stroke basis. Therefore, the hinge functions not only as a flexible joint between the wing and the body

wall of the thorax, but also as an 'organ' with several independent elements (the sclerites). Of these, four, studied by Melis *et al.* in the fruit fly *Drosophila melanogaster*, are connected to a dozen direct flight muscles that together drive the varied wing movements.

Understanding how the joint functions is difficult, because the hinge and its associated muscles are internal structures that can't be observed directly in an insect with flapping wings, and the high frequency of wing beats further complicates matters. As a result, the key questions of how muscle activity generates sclerite movement and, as a consequence, causes changes in wing motion have been challenging to address. Melis and colleagues used an innovative approach to examine the neuroanatomical basis of how the wing hinge functions. The authors recorded the calcium activity (a readout of the cellular activity) of the 12 muscles associated with 4 sclerites and mapped this information onto the fly's wing movements, using machine learning. Their strategy thus provides a glimpse of the potential contribution of individual sclerite–muscle groups to wing motion.

The fruit fly wing hinge has conventionally been studied in dissected tissue in which physical force is applied to each observable muscle and the subsequent effect on wing movement is recorded[3]. Such experiments are, by design, limited to providing results consisting of static interpretations. Although some researchers have recorded muscle activity in live insects, such as blowflies[3,4], and have provided quantitative insights[4,5] into the function of individual muscles, the effect of the collective action of all wing muscles remains unknown.
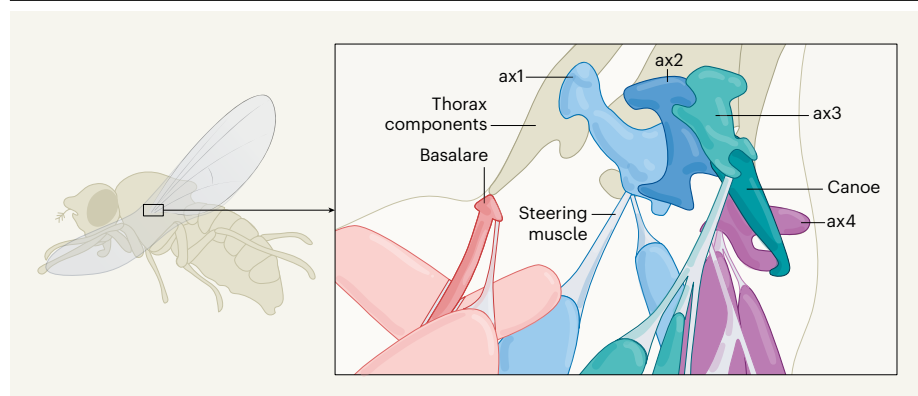
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Figure 1 | The wing hinge of the fruit fly *Drosophila melanogaster*. The fruit fly wing is connected to the insect's body (a region termed the thorax) by a hinge that contains tiny structures called sclerites. These sclerites (named the basalare, ax1, ax2, ax3, ax4 and the canoe) transmit forces from one to the other, resulting in the back and forth motion of the wing. Melis *et al.*[1] investigated how this wing hinge controls wing movements by using imaging to track muscle activation and the associated simultaneous wing movements, and revealed the relationships between the muscles and the wing movements using machine-learning methods. Some of these sclerites (the basalar, ax1, ax3 and ax4) are connected to steering muscles, and the sclerites and muscles together control wing movements. (Adapted from Fig. 1 of ref. 1.)

Simultaneous calcium imaging of all steering muscles has shown that each hinge unit (the sclerite and its associated group of muscles) has two functional set of muscles — a constantly active set and a transiently active one, which together drive wing motion[6]. A technique called X-ray tomography has revealed that a tendon of one steering muscle buckles during the wing's upstroke for wing beats that have high amplitudes, suggesting that contraction of this muscle must be effective mainly during the downstroke and hence activity of this muscle would limit the wing amplitude at the lowest part of the downstroke[7]. Collectively, these approaches have considerably enhanced our knowledge of flight control. However, the biomechanical underpinnings of the musculoskeletal interactions that lead to wing motion during flight remain far from clear.

Melis and colleagues recorded the calcium activity in the fruit fly's steering muscles and simultaneously measured its wing movements. Using a neural-network approach, the authors successfully evaluated and predicted wing movements on the basis of the muscles' calcium activity. Interestingly, Melis *et al.* used a specific architecture of the neural network to map all 13 inputs — 12 for the steering-muscle activities and one for wing-beat frequency — onto output variables that were used to reconstruct 4 angles that defined the wing position and shape. This architecture included an internal 'bottleneck' layer of five nodes, corresponding to the four sclerites and one for the wing beat frequency[8], such that each node receives inputs from its associated muscles, thus building the hinge's biomechanical groups into the neural architecture.

The predicted muscle-activity patterns were used to model wing movements that could simulate short flight sequences, resembling those of a real fly. Using a robotic flapper as a model, the authors tested the aerodynamic effect of controlling the four angles used to define the wing position and shape.

Machine-learning strategies for analysing the neuromechanical principles of joints bring researchers a step closer to building a purely physics-based model that explains how muscle activity causes deformation in the sclerites, which ultimately produces the diversity in wing movement. Crucially, this work provides a computer platform for performing virtual experiments. Melis *et al.* used their model to alter the activity of single muscles and mapped the effects these changes had on wing movements.

In addition to increasing and decreasing the activity of one muscle in their virtual experiments, the authors simultaneously changed the activity in the other muscles in the same proportions as those of the synergies they found in a live fly. It is unclear whether these synergies occur randomly or whether they represent a strategy in which the activities of differing sets of muscles are always coupled. Another possibility is that these muscle groups and sclerites are physically constrained to move in a coupled manner and that, therefore, they must act on the wing in ways that are more limited than the full set of combinations of muscles and sclerites.

The authors not only investigated aspects of wing movement, such as the wing-stroke angle, but also examined changes in the arching of the wing surface (wing camber). The effect of wing camber on aerodynamic output has been debated for years[9], and computer models will help scientists to test whether flies control their wing camber during flight manoeuvres, and if so, how they do this. Results from such computer analyses might also reveal the mechanical basis for the clutch mechanism that has been proposed previously for the wing hinge[10]. Such a system could enable each wing to be independently decoupled from the oscillating thorax during some behaviours, such as courtship, but remain physically connected to each other during others, including flight. During courtship, male *D. melanogaster* extend and vibrate only one wing away from the thorax to generate a mating song; the other is folded and disengaged. Understanding how such physical strains are transferred from the thorax to the wing through the hinge will shed light on how the wings are actively engaged and disengaged during flight.

Previous work on steering muscles indicates that millisecond differences in the firing phase of neuronal inputs into muscles affect their output on a stroke-to-stroke basis[4,11]. However, calcium levels in the muscles, measured by Melis and colleagues using a calcium-indicator protein called GCaMP7f, reveal a relatively slow and integrated signal over time. Although a useful measure of activity, it remains unclear whether such analyses represent the entire behavioural repertoire and whether they can be used to predict a complete map of all the relevant interactions between muscles and the thorax. Moreover, although the authors studied fruit flies, their results might be applicable to other insects, even though each species has its own hinge architecture. For instance, some parts of fly wing hinges (sclerites and steering muscles) are similar to those of bees and wasps[12]. A generalized model with properly adjusted parameters and measurements will enable us to understand the wing hinge as well as its evolutionary importance to the mechanisms for flight control.

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