Gr32a-positive neurons — thereby allowing their activation by capsaicin — to demonstrate the sufficiency of these neurons for eliciting the increased aggression and decreased courtship behaviors.

While these results show the importance of gustatory pheromones in mediating male–male behaviors, how do olfactory cues — also shown to be important in mediating aggression by males — regulate these interactions? The olfactory pheromone cVA has been shown to increase aggression by activation of the olfactory receptor Or67d [13]. Wang *et al.* [1] found that the gustatory receptor Gr32a is necessary for the cVA aggression-promoting behavior, with Gr32a mutant flies showing no increase in aggression when exposed to cVA. By contrast, males with a mutation in the cVA receptor Or67d showed normal levels in aggression in response to 7-T, thus suggesting that the Gr32a pathway is necessary for, or 'gates', the response to cVA, whereas the response to 7-T is independent of cVA (Figure 1B).

Further research has shown that several olfactory receptors respond to odors present in males and females, and one of those receptors, Or47b, has been suggested to be involved in social behaviors such as courtship [19]. To determine whether a similar hierarchical interaction between taste and smell regulates courtship, Wang *et al.* [1] examined the contribution of Or47b in mediating courtship behaviors in the presence and absence of the cuticular hydrocarbon pheromones. They found that the presence of Or47b was critical for promoting male–male courtship when tested with flies lacking the cuticular hydrocarbon pheromones, but the presence of the cuticular pheromones was sufficient to inhibit courtship. It remains uncertain whether the 7-T cuticular pheromone similarly gates the Or47b pathway. Nonetheless, taken together, these results show that the olfactory system cannot on its own affect male–male interactions, but requires the presence of gustatory cues as well. The taste system somehow 'gates' the activity of these olfactory mediated behaviors (Figure 1B).

Rather than going on a series of 'blind dates' with little information about the appropriateness of the other individual, flies use their gustatory and olfactory systems to inform themselves whether they should fight or attempt to mate with another fly. Results from this study [1] are a first step towards showing the particular importance of gustatory pheromones in mediating other chemosensory systems. It brings forward many more questions, including: what are the the neural substrates and circuits involved in 'gating' the olfactory *versus* gustatory systems? Moreover, if gustation is as dominant a sense as it appears, cVA seems to be an almost redundant, unnecessary cue in male–male interactions. What additional information does cVA provide? Finally, previous research has demonstrated that auditory and visual cues are also involved in both courtship and aggression [15,20] — do they similarly inhibit, or are they inhibited by, the gustatory system? Because sensory integration, or 'fusion', is of such fundamental importance for any animal's behavior, such studies will help illuminate the general principles of the neurobiology controlling these behaviors across other taxa.

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Tendon Homeostasis: The Right Pull

Mechanotransduction, the conversion of a biophysical force into a cellular response, allows cells and tissues to respond to their mechanical milieu. How muscle force is translated through TGF-β signaling to regulate tendon homeostasis offers an interesting *in vivo* example of mechanotransduction.

Amnon Sharir* and Elazar Zelzer

Tendon disorders, injuries and degeneration are prevalent and pose a significant health problem [1]. Current understanding of the mechanisms involved in tendon disorders and repair is limited, resulting in relatively poor

success in prevention as well as intervention measures [2]. Tendons are made of connective tissue interposed between muscles and bones and passively transfer force from the former to the latter, thereby making movement possible. Therefore, one of the key challenges in tendon research and medicine is to understand the context-specific role of mechanical stress in their function, maintenance and regeneration.

Mechanical stresses have been shown to serve as informative signals that induce specific biochemical and gene expression changes in almost every tissue and organ [3]. This mechanosensitive feedback requires cells to sense their environment and convert mechanical forces into a molecular response, which in turn activates diverse signaling pathways, a process termed 'mechanotransduction' [4]. Several molecular players involved in this feedback mechanism have already been identified, among them transforming growth factor β (TGF-β). *In vitro* studies showed the coupling between mechanical load and TGF-β in various tissues and organs [5], yet, the *in vivo* picture was less clear. In a recent issue of *Current Biology*, Maeda *et al.* [6] provide intriguing evidence for how mechanical activation of the TGF-β/Smad2/3 pathway regulates the maintenance of tendon extracellular matrix (ECM).

The cellular component in tendons comprises tenocytes, a distinctive type of fibroblast that synthesizes and secretes collagen and other components of the tendon ECM. Adaptation of tendons to various mechanical alternations was the subject of numerous studies. It was found that, in general, added load within physiological limits results in an increase in collagen synthesis, which enhances the tendon's resistance to load [7]. A reduction in stress results in an opposite effect [8].

Evaluation of tendon homeostasis was traditionally based on histological analysis and mechanical testing [9]. However, in recent years progress has been made in the elucidation of the underlying molecular mechanisms. The most prominent finding was that scleraxis (*Scx*), a basic helix–loop–helix (bHLH) transcription factor, is expressed by tenocytes and their progenitors [10]. Moreover, genetic analyses in mice demonstrated the involvement of *Scx* in tendon formation and ECM production [11]. Gene expression screens aimed at revealing the mechanisms that mediate the effect of mechanical stress on tendons have reported an increase in *Scx* transcript expression in loaded tendons, versus a decrease in unloaded ones [12,13]. Now, Maeda *et al.* [6] identify in mice a marked reduction in *Scx* expression following an acute and drastic drop of load from the Achilles tendon, caused by its transection. This system provides a unique opportunity to study the reaction of tenocytes to mechanical manipulations, which simulate common clinical scenarios in tendon pathologies.

After complete transection, the tendon is devoid of tensile load. To establish the relation between mechanical force and tenocyte function, the authors introduce a model of temporarily decreased tensile load in tendons. A temporary decrease in *Scx* expression, a correlated reduction in the secreted ECM components collagen type I and COMP, and an equivalent temporary decline in the tendon's mechanical properties all demonstrate *in vivo* that tendons adapt to changes in their mechanical environment by modifying ECM composition, which in turn affects the tendon's function [7,14]. This chain of causality may explain why exercise is crucial for tendon healing. However, as it was found that both excessive load [15] and its absence impair healing [16], the optimal level of exercise is a critical question in tendon therapy. The finding that a certain amount of shear stress is optimal for tenocyte secretion of ECM components suggests a possible molecular explanation for this phenomenon, which may be used to improve the quality and accuracy of tendon rehabilitation.

Recent studies have implicated TGF-β signaling as a major regulator of tendon development [17,18]. Activation of TGF-β signaling leads to a robust induction of *Scx* and additional tendon markers, including tenomodulin, a type II transmembrane protein and an inhibitor of angiogenesis. Furthermore, disruption of TGF-β signaling in *Tgfb2*/*Tgfb3* double-mutant mouse embryos results in a complete loss of all tendinous tissue. The results of Maeda *et al.* [6] show that TGF-β is also important for homeostasis of mature tendons. TGF-β induces *Scx* expression in tenocytes similarly to mechanical load; hence, mechanical load regulates *Scx* expression through activation of TGF-β (Figure 1). Intriguingly, the idea that physiological levels of secreted TGF-β support *Scx* expression, whereas higher levels cause tenocyte death, corresponds to the clinical situation of overuse pathologies in tendons [15]. Attempts to control ECM composition by targeting TGF signaling have recently been made in tendon clinical practice and in tissue engineering for tendon repair [9,19]. Different members of the TGF family are either removed or added, depending on the situation and the desired outcome [19].

The study by Maeda *et al.* [6] thus offers insight into the relation between mechanical load and bioavailability of

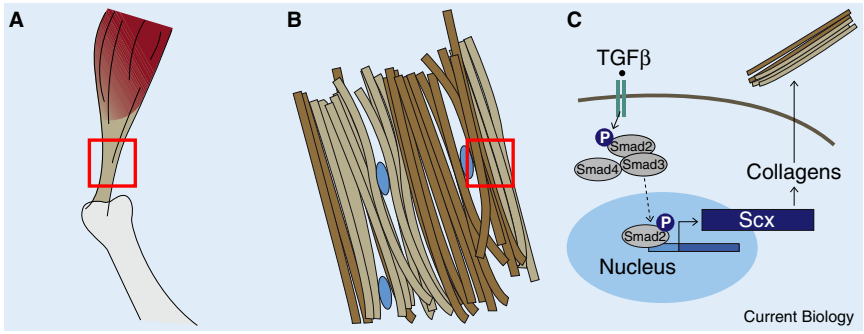

Figure 1. TGF-β signaling regulates tendon homeostasis.
(A) The main function of tendons is to transmit force generated by contracting muscles to the skeleton. (B) The tendon consists of tenocyte cells (in blue) and extracellular matrix (mainly collagen). (C) A conceptual illustration of TGF-β signaling. Upon binding of TGF-β to its receptor, Smads are phosphorylated and translocated to the nucleus, where they act as transcription factors to activate the expression of scleraxis. Scleraxis promotes the synthesis and secretion of collagen and other components of the tendon ECM. B and C are magnifications of the red squares in A and B, respectively (modified after [20]).

TGF-β as a signal that regulates *Scx* expression to increase secretion of matrix components. However, an important question that remains open is how the mechanical signal is translated to activate the TGF-β signaling pathway.

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Innate Immunity: Unfolding the Neuro-Immuno Connections

The innate immune system maintains health and fitness during infection by eliminating infectious agents and by limiting damage caused by pathogens or immune activation. The nervous system contributes to innate immunity by modulating the expression of antimicrobial peptides and by regulating the unfolded protein response.

Man-Wah Tan

Infectious agents can present challenges with life-or-death consequences to eukaryotes. The host has evolved two means of maintaining health and fitness during infection: resistance and tolerance [1,2]. Resistance is achieved by elimination of the source of the problem, either by killing the pathogen or by limiting its growth. Tolerance (not to be confused with immunological tolerance) is effected by limiting the direct damage inflicted on the host by a pathogen or the collateral damage to host tissues caused by the immune response. The concepts of resistance and tolerance, while long-recognized by plant biologists and involving discrete mechanisms of plant defense, are only beginning to be appreciated in studies of animal immunity [2]. Recent studies of host defense in *Caenorhabditis elegans* that have examined immune responses in intact organisms indicate that neuronal signaling regulates resistance and that the unfolded protein response (UPR) contributes to tolerance. A recent study reported in *Science* by Sun *et al.* [3] suggests that tolerance mediated by the UPR also has neuronal origins.

Neural regulation of the insulin-like peptide is well-known and occurs through the insulin-like receptor DAF-2 [4]. Another neuropeptide, DBL-1, activates a transforming growth factor β (TGF-β) pathway and induces antimicrobial peptide expression in the epidermis [5]. Because both the insulin and TGF-β pathways regulate the expression of antimicrobial peptides, they likely contribute to immune function by eliminating the invading pathogens. In contrast, chronic secretion from neuronal dense core vesicles causes immune suppression and increased susceptibility to the human pathogen *Pseudomonas aeruginosa*. This effect is mediated by a neuronal insulin-like peptide, INS-7, which acts on intestinal DAF-2 to suppress the expression of antimicrobial peptides [4]. The importance of this neuro-immuno axis in host defense is underscored by the discovery that *P. aeruginosa* further suppresses antimicrobial gene expression by inducing *ins-7* expression [6].

The UPR consists of a set of three primary responses, which help cells maintain homeostasis when misfolded proteins accumulate in the endoplasmic reticulum (ER). First, protein synthesis and translocation into the ER are lowered. Second, the expression of chaperones that aid in protein folding is increased. Third, the degradative capacity of the cells is increased to eliminate misfolded proteins. UPR signaling is mediated by three distinct and highly conserved