by Li et al. (2014) is controlled primarily by the frequency of translation initiation. Until now, the rules of initiation in bacteria appeared to be fairly simple. The extent of complementarity between the ribosome binding site in mRNA and the rRNA of the small ribosomal subunit is considered the primary determinant for start codon recognition (Shine and Dalgarno, 1974), whereas the mRNA tertiary structure additionally modulates the efficiency of the ribosome-mRNA interaction (de Smit and van Duin, 1990). Applied to individual genes, these simple rules indeed have certain predictive power and have been able to guide optimization of gene expression (Salis et al., 2009). Strikingly, however, the existing models of translation initiation control largely fail to account for the differences in gene expression rates estimated from the ribosome profiling data. It appears that we are still missing some important factors (mRNA binding proteins? regulatory RNAs?) for the accurate prediction of translation initiation rates in living cells. The newly obtained genome-wide knowledge of absolute rates of gene expression provides fertile ground for in-depth bioinformatics analysis of the underlying principles of translation initiation.

The present study exposes important general principles of gene regulation. However, the data also unmask outliers that do not conform to the common rules. For example, although translation of most cistrons does not show signs of premature translation termination, several genes exhibit an abrupt drop in ribosome density. Such unusual behavior may be indicative of yet-unknown translation regulation mechanisms. Another example of noncompliance with the common rule is deviation from proportionality of production of subunits of a small number of stable protein complexes. Do "overexpressed" protein components have some unknown moonlighting functions? Does their rapid turnover play a role in regulation? Exploring these and other odd exceptions may open new doors for better understanding cell biology. We can anticipate that protein accounting, namely the ability to assess the absolute translation rates of cellular polypeptides, will lead to many new discoveries.

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Merkel Cells Are a Touchy Subject

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How the Merkel cell-neurite complex transduces and encodes touch remains unclear. Ikeda et al. now implicate Merkel cells as the primary sites of tactile transduction and the ion channel Piezo2 as the chief mechanotransducer. Surprisingly, Merkel cells also mediate allodynia, providing a new cellular target for chronic pain treatment.

In 1875, Friedrich Sigmund Merkel first described Merkel cells at the base of the skin epidermis, closely apposed to nerve terminals, forming the Merkel cell-neurite complexes (MCN complexes) (Maksimovic et al., 2013). Iggo and Muir later found that the MCN complexes function as slowly adapting type I (SAI) mechanoreceptors that have high spatial resolution and selective sensitivity to edges, corners, and curvatures (Iggo and Muir, 1969). Accordingly, they are proposed to encode object features such as form, shape, and texture (Maksimovic et al., 2013). However, there is a long debate about the way that tactile stimuli are transduced and encoded by MCN complexes. Jumping into this discussion in this issue of *Cell* is the new study by Ikeda et al., showing that Merkel cells transduce tactile stimuli, driving the slowly adapting currents in the nerve terminals within the MCN complex (Ikeda et al., 2014).

Much circumstantial evidence has supported Merkel cells as mechanoreceptor cells. Early EM studies reveal high dense vesicles in Merkel cells and synapse-like structures formed between Merkel cells and nerve terminals (Iggo and Muir, 1969), and more recent studies find voltage-gated Ca^{2+} channels (VGCCs) and the molecular machinery for synaptic transmission (Maksimovic et al., 2013). In *Atoh1/Math1* conditional knockout mice in which Merkel cells fail

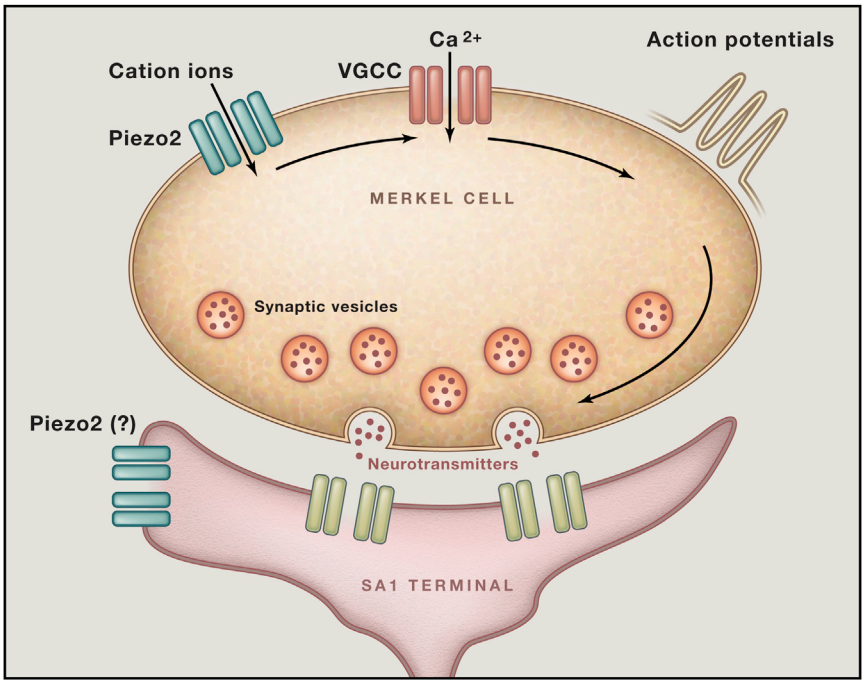

Figure 1. Mechanotransduction by a Merkel-Cell-Neurite Complex
Tactile stimuli activate the mechanically gated ion channel Piezo2 and cause influx of cation ions, which will in turn lead to activation of voltage-gated Ca^{2+} channels ("VGCC"), firing of action potentials, release of neurotransmitters from synaptic vesicles (small dotted circles), and eventual generation of slowly adapting impulses in SA1 afferents. The nature of transmitters and its receptors (green) remains not fully clear. The SA1 terminals may also express Piezo2 and/or other unknown mechanically gated ion channel ("?"), and their direct response to tactile stimuli could be responsible for early dynamic bursting firing that is independent of Merkel cells.

to develop, the SA1 response is absent (Maricich et al., 2009).

However, other studies suggest that mechanotransduction occurs at the innervating myelinated Aβ afferent sites. SA1 afferent units display two phases of discharge in response to indentation onto a touch dome. The dynamic phase (indentation onset) exhibits a burst of action potentials mimicking other types of mechanoreceptors, whereas the static phase (sustained indentation) shows irregular firing that could indicate synaptic transmission (Iggo and Muir, 1969). It has also been noted that the response latency at touch onset is extremely short (0.2 ms) and the afferents are able to generate one-on-one responses to high-frequency stimuli up to 1,200–1,500 Hz for long periods of time (Gottschaldt and Vahle-Hinz, 1981), two features not compatible with chemical communication but instead suggesting direct mechanotransduction at afferent sites. Other studies showed that, although the static SA1 response is abolished by pharmacological blockage of VGCCs or glutamate receptors or upon phototoxic ablation of Merkel cells, initial bursting firing remains intact (Maksimovic et al., 2013; Ogawa, 1996). Collectively, these findings led several investigators to propose the "multiple generators" hypothesis (Iggo and Muir, 1969) or a more concrete two-receptor-site model, in which both Merkel cells and innervating neurites are mechanosensitive (Ogawa, 1996). The study by Ikeda et al. now provides the first direct evidence for mechanotransduction in Merkel cells, mediated by the recently identified mechanically gated ion channel Piezo2 (Coste et al., 2010), and shows that this mechanotransduction is required to drive the SA1 response (Ikeda et al., 2014).

By modifying an ex vivo preparation of whisker hair follicles developed by the Baumann group, Ikeda et al. directly perform patch-clamp recording from Merkel cells (Ikeda et al., 2014). They find that Merkel cells fire slowly adapting action potentials upon injection of small depolarizing current, whereas non-Merkel cells fail to do so. Consistent with the presence of VGCCs, but not voltage-gated sodium channels in Merkel cells (Ogawa, 1996), AP firing is blocked by cadmium (Cd^{2+}) and other VGCC blockers, but not by TTX, a sodium channel blocker. Thus, Merkel cells are excitatory cells capable of firing Ca^{2+} action potentials. They next find that mechanically activated currents in Merkel cells exhibit mixed adaption, containing both rapidly and slowly adapting components. They further show that Merkel cells express Piezo2. Whole-cell currents evoked by mechanical stimulation (MA currents) are attenuated by intracellular injection of a neutralizing Piezo2 antibody or by knocking down Piezo2 expression through Merkel cell infection with a lentivirus expressing Piezo2 shRNA. Collectively, these studies indicate a Piezo2-mediated mechanotransduction in Merkel cells.

Ikeda et al. carry out a series of studies to determine whether Merkel cells transduce natural tactile stimuli and drive SA1 response. Hair movement evokes MA currents and generates APs in Merkel cells, and SA1 response recorded from whisker afferents is eliminated by application of Cd^{2+} or other VGCC blockers, consistent with the suggested roles of Merkel cells in mediating steady-state firing (Ogawa, 1996). A key control is the finding that the SA1 response is unaffected if Cd^{2+} was delivered onto the whisker afferents, away from Merkel cells, consistent with the fact that propagation of APs along innervating myelinated Aβ afferents is dependent on voltage-gated sodium channels that can be blocked by TTX (Ikeda et al., 2014). Furthermore, Piezo2 knockdown in Merkel cells by lentiviral infection leads to attenuation of the SA1 response. Importantly, lentiviral injection into the whisker follicles does not retrogradely infect sensory neurons to affect their Piezo2 expression. Thus, Merkel cells transduce natural tactile stimuli and drive SA1 responses.

In a final set of experiments, Ikeda et al. show that Merkel cells may mediate mechanical allodynia. One hallmark of chronic pain induced by nerve lesions, tissue injuries, or inflammation is the manifestation of allodynia or pain evoked by innocuous mechanical stimuli. Allodynia

can also develop upon skin injection of capsaicin that activates nociceptors expressing the transient receptor potential channel TRPV1 and induces central sensitization in the spinal cord, a process that allows low threshold Aβ afferents to activate pain output neurons (Torebjörk et al., 1992). Ikeda et al. show that, upon subcutaneous capsaicin injection, gentle touch of a single whisker hair leads to a nocifensive reaction that can be blocked by intrafollicle application of Cd^{2+} or by Piezo2 knockdown, suggesting that Merkel cell-mediated mechanotransduction is involved with the expression of mechanical allodynia. To further consolidate this idea, it should be warranted to determine whether mechanical allodynia is impaired in *Atoh1/Math1* knockout mice that lack Merkel cells or in mice in which Merkel-cell-innervating Aβ afferents are removed.

In summary, studies by Ikeda et al. demonstrate that Merkel cells transduce and encode tactile stimuli and drive the SA1 response in innervating Aβ afferents (Figure 1). These exciting findings will certainly open many future studies. First, it should be noted that the data described by Ikeda et al. are not inconsistent with the two-receptor-site model discussed above. Although the static SA1 response was abolished or greatly reduced following Cd^{2+} application or upon Piezo2 knockdown in Merkel cells, the initial bursting firing at the dynamic phase was much less affected, in agreement with previous reports (Ogawa, 1996). Indeed, a recent study showed that Merkel cells are innervated by VGLUT3 lineage neurons that express Piezo2 (Lou et al., 2013), suggesting that direct mechanotransduction may occur at both innervating afferents and Merkel cells. Another recent study reveals two types of Merkel-cell-innervating sensory neurons, marked by differential expression of neurotrophin receptors, TrkC versus Ret/TrkA (Niu et al., 2014). It will be interesting to determine which type(s) of innervating afferents mediate(s) dynamic and/or static discharges. Second, Merkel cells express a range of fast and modulatory transmitters (Maksimovic et al., 2013), and determining how these transmitters are released in response to tactile stimuli and what roles they play in generating the SA1 response warrants study. Finally, the release of modulatory transmitters by Merkel cells might impact nearby unknown sensory terminals. As a result, it remains unclear whether capsaicin-evoked allodynia is mediated through SA1 or other unknown afferents. Regardless, this study raises an unexpected possibility that Merkel cells could be targeted for chronic pain treatment.

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