from being generated by a single genotype [9]. In reality, however, we usually do not know enough about the underlying genetic basis of the traits under study to clearly distinguish between these alternatives. The promise of these new nematode species is that, together with the great breadth of diversity across the group, the specifics of the developmental system can be uncovered so as to allow these broader questions to be addressed.

In some sense, each new fig is like mini Galapagos Island, but rather than being colonized by finches that speciated to fill available ecological roles, these nematodes have specialized to fulfill currently unknown roles within the fig by switching their developmental systems to generate very different feeding structures and head morphologies. Why we do not see an infinitely plastic Darwin's finch fulfilling every ecological role in the Galapagos is undoubtedly explained by a balance between the functional requirements of developmental specialization, the temporal resolution of the environmental variation relative to the generation time of the species and the intensity of natural selection for plasticity in the face of this environmental variation. Why these three different species of nematodes show exactly five different types of heads inside a single fig is undoubtedly rooted in this same balance.

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GPCR Signaling: β-arrestins Kiss and Remember

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β-arrestin-dependent activation of the ERK MAP kinase downstream of GPCRs typically originates from internalized receptor–β-arrestin–ERK complexes. A new study now reports that β-arrestin 2 is sufficiently 'primed' after 'kissing' the β_1-adrenergic receptor to initiate ERK activation even in the absence of formation of the receptor–β-arrestin–ERK complex and receptor internalization.

G-protein-coupled receptors (GPCRs) sense an incredibly diverse range of signals and participate in almost every physiological process in our body [1]. Not surprisingly, they are targeted by a large majority of prescription drugs currently available in the market, such as ARBs (angiotensin receptor blockers), β-blockers and anti-allergy medication [2]. The human GPCR family consists of approximately 800 members that are typically characterized by a highly conserved seven transmembrane topology. Interestingly, the signaling and regulatory mechanisms of GPCRs are mostly conserved throughout this large receptor family. In the classical paradigm, activation of GPCRs with agonist (i.e. activating ligand) leads to coupling and activation of heterotrimeric G proteins, followed by second messenger generation and downstream signaling. In order to put a brake on G-protein signaling, activated receptors are phosphorylated by GPCR kinases (GRKs), which triggers the recruitment of β-arrestins, leading to receptor desensitization, presumably by blocking G-protein coupling through steric hindrance [3]. β-arrestins were then also found to promote clathrin-mediated internalization of GPCRs by interacting with and scaffolding various components of the clathrin-mediated endocytosis machinery [4].

A somewhat surprising finding that emerged about a decade ago and, since then, has been well established and has become an integral part of the current GPCR signaling paradigm is the ability of β-arrestins to act as G-protein-independent signal transducers

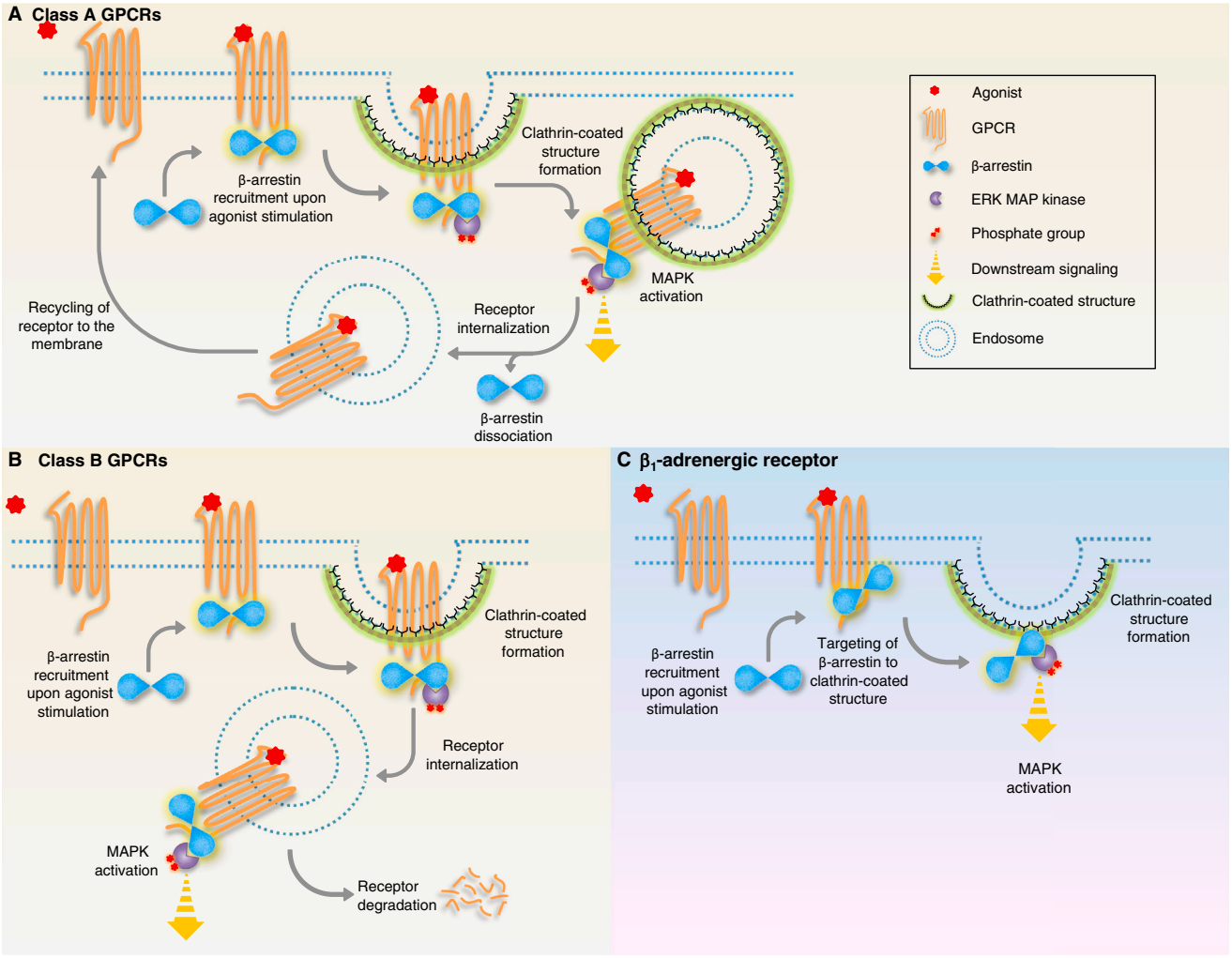

Figure 1. Diverse patterns of β-arrestin-mediated ERK activation downstream of GPCRs.
(A) For class A receptors, agonist stimulation leads to β-arrestin translocation to the plasma membrane, colocalization and internalization of the receptor–β-arrestin complex and ERK activation. β-arrestin interaction with the receptor is transient: it dissociates from the internalized complex followed by rapid recycling of the receptor to the plasma membrane. (B) Class B receptors are associated with β-arrestin more robustly, internalize with β-arrestin and are targeted to endosome as a stable complex with β-arrestin. (C) β_1AR exhibits a pattern that is distinct from both class A and B receptors, whereby β-arrestin 2, after its brief encounter with activated receptor, is localized in clathrin-coated structures at the plasma membrane and triggers ERK activation. β_1AR does not colocalize with β-arrestin 2 in these structures [7].

downstream of GPCRs [5]. Activation of the MAP kinase ERK has become an archetype of this G-protein-independent β-arrestin signaling: β-arrestins scaffold various components of the ERK cascade, bringing them into proximity to promote ERK activation [6]. For several receptor systems that have been used to dissect the spatiotemporal pattern of β-arrestin signaling and its mechanistic basis, receptor endocytosis and ERK activation appear to be coupled events [6]. That is, formation of a complex consisting of receptor, β-arrestin and ERK on internalizing clathrin-coated vesicles appears to be the originating point of ERK activation (Figure 1A,B). A new study published in *Nature Cell Biology* now demonstrates that a brief interaction of β-arrestin 2 with the GPCR β_1-adrenergic receptor (β_1AR), followed by targeting to clathrin-coated structures (CCSs), in the absence of any detectable receptor–β-arrestin–ERK complex formation or receptor internalization, is sufficient to elicit ERK activation (Figure 1C) [7].

β_1AR is expressed predominantly in cardiac tissues and is one of the primary adrenergic receptors for catecholamines, including epinephrine and norepinephrine, and a key mediator of cardiac output [8]. Although β_1AR couples to β-arrestin in the response to agonist stimulation and activates β-arrestin-dependent ERK signaling, it shows low levels of internalization. In order to better understand this intriguing and somewhat divergent behavior of β_1AR compared with other GPCRs, Eichel *et al.* [7] set out to examine the post-activation localization of activated β_1AR, β-arrestin 2 and clathrin using high-resolution microscopy approaches. As expected, the authors observed

that, in response to agonist stimulation, β_1AR leads to ERK activation in a β-arrestin-2-sensitive manner, despite being very poorly clustered at the plasma membrane and not getting internalized. Interestingly, however, stimulation of β_1AR was sufficient to robustly drive the punctate appearance of β-arrestin 2 at the plasma membrane where it colocalized with clathrin clusters in CCSs. This surface translocation of β-arrestin 2 is indeed driven directly by β_1AR stimulation as confirmed genetically (by comparing the response in cells with and without receptor overexpression) and pharmacologically (using treatment with a β_1AR subtype-selective ligand, antagonist blockade and ligand–receptor occupancy). Lack of β_1AR colocalization with surface-translocated β-arrestin 2 in CCSs is surprising and reflects a divergent pattern compared with other GPCRs. Furthermore, restricting the lateral immobilization of β_1AR using antibodies does not impair agonist-induced translocation of β-arrestin 2 to CCSs. This finding suggests that a brief interaction of β-arrestin 2 with agonist-activated β_1AR is indeed sufficient for its targeting to CCSs and that a stable physical interaction with the receptor is not essential. Moreover, treatment of cells with Dyngo-4, an inhibitor of dynamin and of clathrin-coated vesicle scission, does not exert a negative impact on β-arrestin-2-sensitive ERK activation. This observation confirms that β-arrestin 2 can indeed trigger ERK activation while localized in CCSs at the plasma membrane, even when not in a direct physical complex with the receptor, and that physical scission of these CCSs as internalized vesicles is not a prerequisite. Taken together, this set of observations reveals a new framework for β-arrestin-dependent ERK activation. One potential caveat, however, with this study is that it is carried out in transfected cell lines with overexpression of modified receptor and β-arrestin 2 and the *in vivo* significance of these findings therefore remains to be demonstrated. However, it should be noted that experimentation along these lines, especially at the endogenous levels of receptors, remains technically very challenging with currently available tools.

GPCRs are broadly grouped into two classes (class A and B) based on their interaction pattern and affinities for β-arrestins [9]. Class A receptors exhibit a transient interaction with β-arrestins and, after internalization, they are rapidly recycled back to the plasma membrane (Figure 1A). Class B receptors, on the other hand, display robust β-arrestin interaction, exhibit slow recycling and they are targeted to endosomes for subsequent degradation (Figure 1B). For both of these classes, receptor internalization appears to be linked to β-arrestin-dependent ERK activation through the formation of a receptor–β-arrestin–ERK complex [6]. Based solely on its transient interaction with β-arrestin, β_1AR could be classified as a class A receptor; however, the high-resolution microscopy analysis by Eichel *et al.* [7] demonstrates that β_1AR is mechanistically very different from other class A receptors. In fact, under the same experimental set-up, β_2AR — another subtype of β-adrenoceptor and a prototypical example of a class A receptor — exhibits robust internalization and colocalization with β-arrestin 2 in CCSs. These findings raise the interesting possibility that, within the crude classification of class A vs. class B, there might exist additional layers of receptor–β-arrestin interaction patterns that could be uncovered using high-resolution microscopy approaches.

A key question that arises and has not been answered in this study is what is the mechanistic basis of the ability of β-arrestin 2 to signal from CCSs even in the absence of colocalization of β_1AR? It appears as if, once exposed to the activated receptor, β-arrestin 2 can retain a little 'memory' of its activation, perhaps through retention of some activation-dependent conformational changes. Such a 'conformational memory' is sufficient to drive its localization to CCSs at the membrane, presumably through a physical interaction with clathrin, and trigger ERK activation. The conformational dynamics of β-arrestins are known to be quite broad and they are capable of sampling a range of conformational ensembles [10,11]. Still, direct evidence for conformational memory remains to be documented. Another interesting possibility is that β_1AR activation merely serves as a mechanism for surface targeting of β-arrestin 2 and, once there, β-arrestin 2 can localize to CCSs and activate ERK signaling. In fact, a previous study that used a small-molecule dimerizing agent to target β-arrestin 2 to the plasma membrane revealed that the receptor can be entirely dispensable for some level of ERK activation, albeit with slower kinetics [12]. In addition, β_1AR is one of the few GPCRs that can transactivate epidermal growth factor receptor (EGFR) upon agonist stimulation and this transactivation appears to be mediated by β-arrestins [13]. Therefore, further investigation along the lines of β_1AR-induced EGFR transactivation might also reveal some mechanistic clues about the divergent behavior of β_1AR reported by Eichel *et al.* [7]. Nevertheless, irrespective of the exact mechanism involved, this study delineates a new axis of β-arrestin signaling that goes beyond the current framework of class A and class B GPCRs.

Another key issue that remains to be explored further is the generality of this observation. Agonist-induced phosphorylation of serine and threonine residues, both in terms of total number and specific positioning, is a key factor in determining the spatiotemporal pattern of β-arrestin recruitment and its conformation [14,15]. There are several GPCRs that contain either a relatively short carboxyl terminus or very few phosphorylatable residues in their carboxyl terminus. Therefore, it is plausible that such receptors might also display a very transient interaction with β-arrestins and low levels of internalization yet might still exhibit ERK activation through a similar mechanism as described for β_1AR.

One of the remarkable features of the GPCR family has been the overall conservation of signaling and regulatory mechanisms. Studies like this recent paper underline exciting examples of receptor-specific 'variations on a theme' and highlight the range, complexity and versatility associated with the GPCR signaling system. Discoveries like this, which deviate from typical signaling frameworks, also suggest that we still have a long way to go before we can fully appreciate all the possible ways in which GPCR signaling can be fine-tuned.

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Cognitive Neuroscience: The Neural Basis of Motor Learning by Observing

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Somatosensory feedback from the limbs plays an essential role when we learn to make new movements. A recent study shows that motor learning can be accomplished purely through observation, and motor learning by observing also critically depends on the brain's somatosensory system.

Flip through any neuroscience textbook and you'll find colorful maps of the brain neatly dividing the cortical surface into functions. In most cases, blobs of cortical tissue thought to be involved in perception rarely if ever overlap with blobs involved in motor control. The impression these pictures give is that perception and action invoke neural operations that are entirely separable. However, recent work in cognitive neuroscience has blurred the textbook lines between representations of sensory and motor processes in the brain. A new paper in this issue of *Current Biology* by McGregor and colleagues [1] provides further evidence for a sophisticated *sensorimotor* system for motor learning via observation of others' motor learning. Although initially driven by vision, this system seems to rely on somatosensory areas in the brain — areas essential for actually performing motor learning.

Interest in the neural overlap between perception and action has grown, in part, from the early-90s discovery of neurons that have both perceptual and motor properties. Mirror neurons, first noted in the premotor cortex of macaque monkeys, fire during both movement execution and the observation of similar movements [2]. Since their discovery, functional neuroimaging work in humans has demonstrated that action observation activates an extensive network of perceptual and motor areas well beyond the occipital lobe's visual centers [3,4] (Figure 1). Supporting this work, behavioural studies have causally linked the brain's motor areas to perception [5,6], and perceptual learning has been shown to drive improvements in motor learning and neural changes in the brain's motor systems [7]. While many have hypothesized that the sensorimotor systems revealed by these and related tasks might play a role in high-level behaviors such as empathy and