of 426 individuals from 50 ethnolinguistic groups in Africa. H3Africa discovered more than three million variants[13] — mainly in previously unrepresented ethnolinguistic groups. It also observed complex patterns in mixing of ancestries and identified 62 regions of the genome that have been evolutionarily maintained at high frequency, perhaps because of protective roles in viral immunity, DNA repair and metabolism.

These findings highlight — as we and others[8] have argued for years — the need to increase diversity in genome science (Fig. 1). Clearly, Eurocentric studies will not be broadly applicable to all populations. Some disease risk variants are specific to certain populations, and polygenic risk scores (which quantify the risk that an individual will develop a given trait or disease, based on the aggregate or sum of variants they carry) might not generalize well across multiple populations[9,14–16]. Type 2 diabetes is a common disease that demonstrates this observation. Despite a set of well-known risk variants that are shared across populations, seemingly population-specific variants have been identified in East Asian, Mexican and African groups[15,16].

Understanding how differences between our genomes cluster according to the ancestral backgrounds of individuals and groups is undoubtedly valuable. However, inferred clusters might not overlap with social descriptors such as 'Black', 'Latino', 'Asian' and 'European' — an assumption that has been used by some to justify racial categorization[17]. The best evidence so far suggests that social categories and genetic clusters are inconsistent[17,18]. Indeed, one study[19] that identified 21 global ancestries reported that its 6,000 individuals had, on average, DNA from 4 ancestries. This indicates the need for caution when using labels such as African/Black, Hispanic/Latino, Asian or European/white in genome science. Indeed, the use of these terms in genome science should be discouraged except as self-reported descriptors or to provide socio-demographic context. Using these terms risks distorting our understanding of the distribution of HGV in history and health.

In future, we will increasingly use genomics to understand our evolutionary history, predict individual disease risks, develop therapeutics such as vaccines, and cure diseases including sickle-cell anaemia using DNA-editing technologies. To fully realize these expectations, we must address several continuing challenges, including, but not limited to, three factors related to diversity. The first is increasing the participation of individuals from diverse ancestral backgrounds in genome research. This challenge is being met through support for genomics research and capacity building from both large consortia (such as the H3Africa consortium) and national genome projects in under-studied populations. The second is developing global collaborations to establish crucial inter-country biomedical infrastructure, ethical frameworks and equitable data sharing — common barriers to international collaboration. The third is equitable deployment of genomic advances to avoid exacerbating health disparities, especially in resource-challenged settings across the world.

Achieving these goals will greatly improve our knowledge of human genetic diversity, aid disease-gene discovery efforts and facilitate our understanding of human biology. The road from one genome reference to hundreds of thousands of genomes has provided unprecedented insight into human genetic variation and the complex tapestry of our ancestry, leading to many practical scientific and medical benefits. Making these benefits available to all humanity is the next frontier.

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Metabolism

New-found brake calibrates insulin action in β-cells

Rohit N. Kulkarni

Insulin is produced by pancreatic β-cells. The identification of a regulator of insulin signalling in these cells cements the long-standing idea that this pathway has a key role in β-cell biology. **See p.326**

It is almost a century since insulin was first used to treat diabetes[1]. Since then, a great deal has been learnt about the complex metabolic pathways that are regulated by insulin and the related molecule insulin-like growth factor 1 (IGF1), acting through receptor proteins (reviewed in ref. 2). But it is less clear how the activity of these receptors is regulated in the cells that actually produce insulin, the pancreatic β-cells. Such knowledge is urgently needed because reduced β-cell function is a key contributor to diabetes. Deciphering the molecular pathways that regulate β-cells might therefore help to better manage, or even prevent, this disease. On page 326, Ansarullah *et al.*[3] identify a previously unknown regulator of β-cells, and outline the mechanism by which this protein can 'tailor' expression of the insulin receptor.

First, the authors analysed levels of messenger RNA in mouse cells, to identify genes that were highly expressed specifically in the embryonic pancreas. This revealed an abundantly expressed mRNA encoded by a gene on chromosome 3. The corresponding human gene is named oestrogen-induced gene (*EIG121*), and the mouse and human proteins are highly evolutionarily conserved.

Ansarullah *et al.* renamed the protein insulin inhibitory receptor (inceptor), because of its similarities to the insulin and IGF1 receptors. All three receptors span the cell membrane and have similar extracellular domains. But, unlike the insulin and IGF1 receptors, the short cytoplasmic tail of inceptor carries an amino acid sequence known to bind to the assembly polypeptide 2 (AP2) protein complex. AP2 is involved in a process called clathrin-mediated endocytosis, through which molecules and receptors at the cell surface are transported into the cell.

Then, the authors examined the function of inceptor by generating mice completely lacking the inceptor gene, and mice in which the gene could be deleted specifically in β-cells. The two models show generally similar traits.

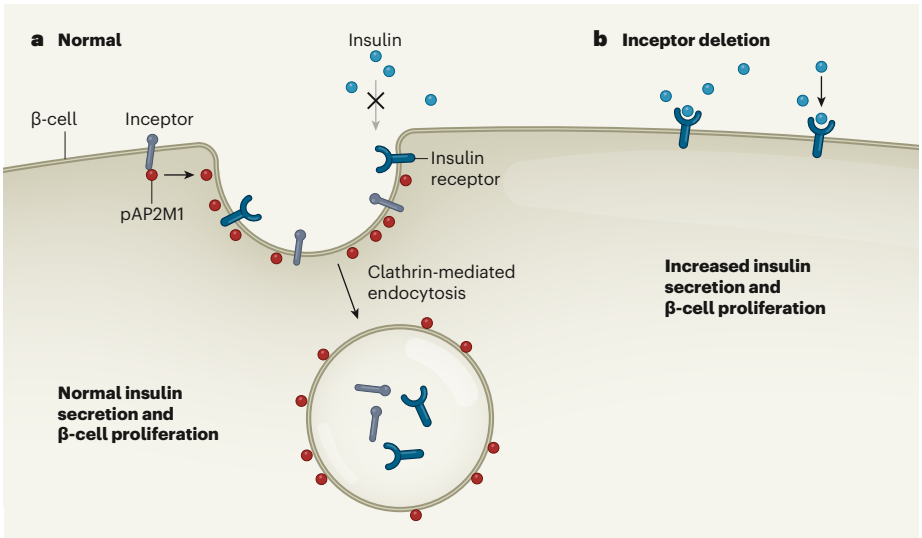

Figure 1 | A newly discovered regulator of insulin signalling. Insulin is produced in and secreted from pancreatic β-cells, but it has been unclear how insulin signalling is regulated in these cells. Ansarullah *et al.*[3] have discovered a previously unknown regulator of insulin signalling in β-cells, the protein inceptor. **a**, The group finds that inceptor binds to pAP2M1, a subunit of the AP2 protein complex. This triggers a process called clathrin-mediated endocytosis, in which inceptor and insulin receptors (along with the related insulin-like growth factor 1 receptors, not shown) are engulfed by the cell membrane and enter the cell. Insulin therefore cannot bind to its receptor. This insulin desensitization restrains insulin signalling to fine-tune insulin secretion from, and proliferation of, β-cells, maintaining normal responses to glucose. **b**, Deletion of inceptor prevents internalization of insulin receptors through this pathway, thereby allowing unrestrained insulin action and leading to enhanced insulin secretion and an increase in β-cell proliferation.

These include low glucose levels in the blood, along with enhanced insulin secretion compared with controls in the period immediately after an increase in blood glucose levels (after a meal, for instance, known as first-phase secretion), and a higher capacity to respond to increased blood glucose levels (improved glucose tolerance). The idea that inceptor acts mainly in β-cells is supported by the observation of greater β-cell proliferation and mass in both strains of mutant animal compared with controls, indicating that the mutant β-cells contain more insulin. And when the pancreatic tissues rich in β-cells were grown in culture, those of the mutant animals showed higher activity of the protein p-Akt, which is activated by insulin/IGF1 receptor pathways, than did the controls. Together, these data indicate that inceptor acts to directly calibrate the expression of the insulin receptor and thereby contributes to maintaining healthy glucose levels.

These findings are complementary to scientific reports from several decades ago, which argued that insulin has a physiological role in β-cells[4,5]. Indeed, deletion of the insulin receptor in β-cells (a modification dubbed βIRKO) in mice leads to traits[5,6] that are the opposite of those seen in Ansarullah and colleagues' β-cell-specific mutant mice. For example, βIRKO mice show a blunted first-phase secretion leading to glucose intolerance[5], which arises owing to effects specifically in the mutant β-cells[6]. The data also align with several studies using *ex vivo* and *in vitro* models that demonstrate a direct role for insulin signalling in β-cell biology[7–11]. β-cells lacking functional insulin or IGF1 receptors, or lacking other proteins regulated by these receptors, manifest diverse defects, including reduced expression of the protein PDX1, which controls β-cell maturation and secretory function. Lowered PDX1 expression leads to altered growth of β-cells and blunted glucose-stimulated insulin secretion[2,6,12–15].

Ansarullah *et al.* went on to further investigate whether inceptor might densensitize β-cells to insulin through its interactions with AP2. They found that inceptor interacts with pAP2M1, the active form of the AP2M1 subunit, to aid clathrin-mediated endocytosis of the insulin and IGF1 receptors. Once in the cell, they cannot be activated by insulin (Fig. 1).

The fact that inceptor can desensitize β-cells to insulin in this way has implications for questions that have dogged the field for decades: what are the levels of insulin that surround human β-cells in the fasting and post-feeding states, and how is insulin-receptor signalling in β-cells affected in diabetes, when cells across the body fail to respond to insulin? It is sometimes assumed that local insulin levels around β-cells must be high, but there are virtually no experimental data that confidently provide the precise dynamic concentrations of insulin at the surface of the β-cells *in vivo* in mammals.

A related mystery is the location of the insulin receptor on β-cells. If it is located at the cell's basolateral surface, it would be close to systemic vessels, enabling it to be activated by insulin circulating in the blood. By contrast, its presence at the opposite, apical side might mean it was modulated by insulin secreted from surrounding β-cells (known as paracrine regulation). A basolateral position is supported by the observation that injected insulin has direct beneficial effects on human β-cells[16], and that these benefits are lost in people who have type 2 diabetes[16,17]. The identification of inceptor should now prompt fresh studies to re-examine the potential role of insulin in paracrine regulation.

Although the identification of inceptor undoubtedly advances our understanding of insulin signalling, several questions remain. For example, how do metabolic regulator molecules such as hormones, metabolites and stressors affect the expression and function of inceptor in β-cells, as well as the hypothalamic–pituitary–gonadal axis that controls reproduction and immunity, tissues of which also express inceptor? Are there genetic variants in or near the inceptor gene that are associated with diabetes or metabolic diseases? Insulin signalling has been shown to directly[18] and indirectly[19] regulate gene expression — it would be worth contemplating how interactions between inceptor and insulin receptors might alter these nuclear effects of insulin signalling. Finally, changes in the patterns in which methyl groups are added to mRNA have been found in β-cells in people who have type 2 diabetes[20]. What part might modifications of inceptor mRNA play in altering β-cell biology?

The identification of inceptor cements the legacy of insulin action in β-cells. The protein's discovery warrants a renewed focus on finding ways to harness proteins in the insulin signalling pathway in β-cells, with the long-term goal of more effective management of — or even a cure for — diabetes.

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Spinal cord injury

Neuroprosthetic device to maintain blood pressure

Patrice G. Guyenet

The inability to maintain blood pressure is a debilitating consequence of spinal cord injury. This problem has now been circumvented, by artificially recreating a reflex essential for blood-pressure stability. **See p.308**

Paralysis and sensory deficits are the most obvious consequences of spinal cord injury (SCI). But many people also experience orthostatic hypotension – an inability to maintain blood pressure when moving from lying to sitting or standing[1]. In the short term, the condition can prevent normal filling of the heart with blood, and can cause light-headedness and dizziness. In the long term, recurrent episodes of orthostatic hypotension increase the incidence of heart attack and stroke, which are leading causes of death in people who have had an SCI. On page 308, Squair *et al.*[2] report a neuroprosthetic strategy that minimizes orthostatic hypotension caused by SCI. The device restores blood-pressure control in rodents, monkeys and humans.

Gravity causes blood to pool in the lower part of the body when we sit or stand. Orthostatic hypotension results mainly from the impairment of reflexes that prevent this pooling. The most crucial of these is the baroreflex, which is initiated by baroreceptors – neurons that sense arterial blood pressure and the degree of filling of the large veins and heart chambers[3]. In mammals, these sensors are active when the body is at rest. A reduction in arterial blood pressure or blood volume reduces baroreceptor activity. This, in turn, activates the sympathetic branch of the autonomic nervous system, restoring blood pressure by increasing vascular resistance and the flow of blood back to the heart[4]. SCI interrupts the connection between the lower brainstem, which receives the information from the baroreceptors, and the sympathetic neurons that innervate the cardiovascular system, which originate from thoracic and upper lumbar spinal segments (Fig. 1).

Orthostatic hypotension is typically managed by lifestyle changes (such as using compression bandages on the legs and sleeping in a semi-upright position) and drugs such as fludrocortisone (a blood-volume expander) or midodrine (which activates the receptors that normally mediate the effect of the sympathetic nerves on the heart and vascular muscles)[5,6]. However, these drugs can have untoward effects. Other approaches include electrical stimulation of skeletal muscles in the lower limbs, which activates the muscle pump and aids cardiac filling, and abdominal constriction belts. Both of these strategies have been used therapeutically, but their effectiveness has not been clearly demonstrated[6].

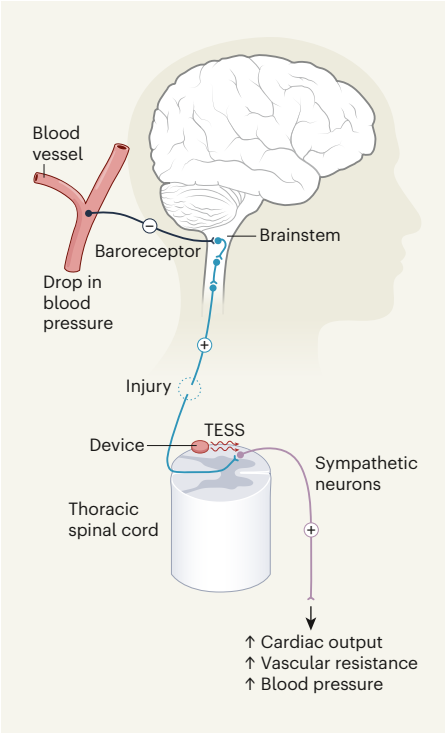

Figure 1 | Replicating the baroreflex. The baroreflex controls blood pressure in mammals. A drop in blood pressure reduces the activity (minus symbol) of neurons called baroreceptors, ultimately leading to the activation (plus symbol) of brainstem neurons that directly innervate and activate sympathetic neurons in the spinal cord. But spinal cord injury severs this connection, preventing the baroreflex from working properly. Squair *et al.*[2] designed a neuroprosthetic device that can circumvent this problem. If blood pressure falls, the device delivers an electrical stimulus called targeted epidural spinal stimulation (TESS) to the back side of the thoracic spinal cord to activate sympathetic neurons (albeit by a different route from that used by the natural baroreflex; route not shown). The sympathetic neurons send signals to the heart and blood vessels to increase cardiac output and vascular resistance, thereby restoring normal blood pressure.

Could neuroprosthetic devices be a better alternative? The principle is to restore function by electrically stimulating the neural pathways that have become unresponsive as a result of SCI. Ideally, the stimulation should closely approximate the pattern of activity that normally controls the targeted function. Such an approach has already been used to partially restore locomotion in primates[7]. It has also been used to activate the leg muscles to improve blood-pressure control in people with an SCI[8], although the reasons for its apparent success in this setting were unclear.

Squair and colleagues set out to develop a more precise neuroprosthetic for blood-pressure control. Their starting point was the development of a rat model of SCI. Analysis of neuronal activity in the model confirmed that blood pressure and sympathetic responses were unstable in these animals. Owing to their small size, the rats did not experience orthostatic hypotension. However, the authors used a negative-pressure chamber to reduce air pressure around the lower body; this caused blood to pool in the lower body, replicating the phenomenon.

Next, Squair *et al.* asked where electrical stimulation (called targeted epidural spinal stimulation, or TESS) should be applied to trigger the sympathetic responses that alter blood pressure. They systematically stimulated spinal segments in the injured rats, and found that the animals' blood pressure could be raised substantially by delivering electrical pulses close to the back side of the lower thoracic spinal cord. An impressive series of experiments – imaging and anatomical analyses, combined with computational modelling and manipulations to activate or inhibit neurons involved in the region – revealed that TESS elevates blood pressure by activating a subset of sensory afferent neurons (which transmit signals from the skin, muscles and internal organs towards the spinal cord). These afferent neurons indirectly excite the efferent sympathetic neurons that control the splanchnic circulation (the blood vessels of the abdominal organs).

The authors' next, highly original, step was to design a biomimetic control device that continuously adjusted TESS to prevent any blood-pressure drop in the injured rats. They then went on to successfully adapt this 'prosthetic baroreflex' concept for rhesus