the cage opened, breaking most of its contact with the growth factor. By contrast, applying the force through α_V caused this subunit to unfold before any major structural changes to the pro-domain occurred. These results suggest that force application in the correct orientation — that is, through the region of the pro-domain that contacts β_6 — is essential for opening the cage.

And it seems that nature has specifically engineered integrins this way. As the authors noted, all subdomains in β integrins are connected to adjacent subdomains by two covalent bonds, whereas in α integrins they are linked through a single bond. This ensures that force is securely transmitted through β integrins, and that α integrins are prone to failure. Because TGF-βs and integrins arose during the same evolutionary period and in the same phylogenetic branch, the mechanism of force-induced TGF-β1 activation is probably shared across many species. However, unlike TGF-β1 and TGF-β3, the pro-domain of TGF-β2 lacks a recognizable integrin binding motif such as RGD (ref. 1). The mechanism by which TGF-β2 is released from its cage is unknown.

Much remains to be understood about TGF-β uncaging. Because Dong *et al.* used very high forces in their simulations, they could not determine the minimum force required to release TGF-β1. Certain more-subtle changes to the pro-domain structure would probably be sufficient for uncaging. Would $\alpha_V\beta_6$ remain bound to the pro-domain at these forces, as it did in the simulations, or is the binding seen in the simulations an artefact of the extreme forces used? Answering this question will provide a key test of the current model, because the unbinding force between the integrin and the pro-domain should be as high or higher than the force required to open the cage. To address this issue, single-molecule methods could be used to directly measure forces across integrins during unbinding and uncaging[7,8].

The method used by the authors to detect TGF-β1 involves measuring the activity of the released growth factor, and as such is indirect, with low time resolution and sensitivity. By contrast, the role of integrins in another process (remodelling extracellular matrices) can be directly examined at single-cell resolution using fluorescence-based methods[9]. If a similar resolution could be achieved for TGF-β activation, it would allow researchers to determine whether the released growth factors are used by the cells that do the uncaging or by the surrounding cells.

More broadly, Dong and colleagues' structure is a major leap forward in our understanding of how integrins interface with the extracellular environment. This should and will inspire researchers to ask deeper and more difficult questions about the links between mechanical and chemical communication between cells. ■

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EARTH SCIENCE

Making a mountain out of a plateau

A theory proposed in 2015 suggested that relatively flat surfaces in mountain ranges were formed by the reorganization of river networks. A fresh analysis rebuts this idea, reigniting discussion of a long-standing problem in Earth science.

HUGH SINCLAIR

The origin of low-gradient surfaces in mountain ranges has long generated debate. The conventional explanation involves the acceleration of river incision into a pre-existing and slowly eroding low-gradient landscape[1], caused by a change in the underlying geological or climatic controls on the carving of mountain topography. However, a new model has been proposed[2] that invokes the expansion and contraction of river networks during mountain building, and which does not require a change in the underlying controls. Writing in *Geology*, Whipple *et al.*[3] challenge this model, particularly in its application to the mighty gorges of the Yangtze, Mekong and Salween rivers in southeastern Tibet. The authors defend the conventional idea that these rivers have incised into a relatively low-gradient landscape that is a remnant of a once larger Tibetan Plateau[4].

The formation of mountain landscapes requires the uplift of rock, usually caused by colliding tectonic plates. Rock uplift is then countered by the incision of valleys by rivers and glaciers, and the coupled erosion of hill slopes. In steep mountain regions in which rates of erosion are comparable to those of rock uplift, river incision into rock undercuts mountain slopes, forcing the episodic collapse of the hill slopes through landslides and debris flows. This drives many mountain slopes towards steep gradients ranging between 20° and 45°, determined by rock strength[5]. In this context, understanding the presence of extensive surfaces that have anomalously low slopes within many mountain ranges (such as the Rockies[6], Himalayas[7] and Pyrenees[8]) is an ongoing challenge.

The suggestion by Yang *et al.*[2] that many of these surfaces resulted from the inevitable expansion and contraction of river networks — more specifically, from changes in the plan-view geometry of river networks — is therefore an intriguing theory that needs testing. Crucial to the proposed process is the migration of drainage divides, the ridges that separate neighbouring river catchment areas. The resulting expansion and contraction of catchment areas leads to increases and decreases, respectively, in the amount of precipitation and run-off that feeds the water discharge of main 'trunk' rivers.

Changes in water discharge drive changes in the capacity of a river channel to transport sediment and incise into underlying rock. As one river catchment captures an area of water drainage from another, the capturing river's ability to incise increases, driving erosion. By contrast, the catchment that is the victim of capture loses drainage and so becomes less able to incise. This can cause river channels to accumulate coarse sediment and reduce the gradient of hill slopes below the threshold for landsliding, enabling the slopes to increase their soil cover. This conversion of victim catchments[9] to low-gradient landscapes is the alternative mechanism proposed by Yang *et al.* for the formation of low-gradient surfaces in mountain ranges.

Whipple and colleagues focus the debate around the extraordinarily elongated rivers that drain the eastern margin of Tibet. The unusual geometry of this network, in which parallel river gorges run in close proximity, is thought to result from regional crustal

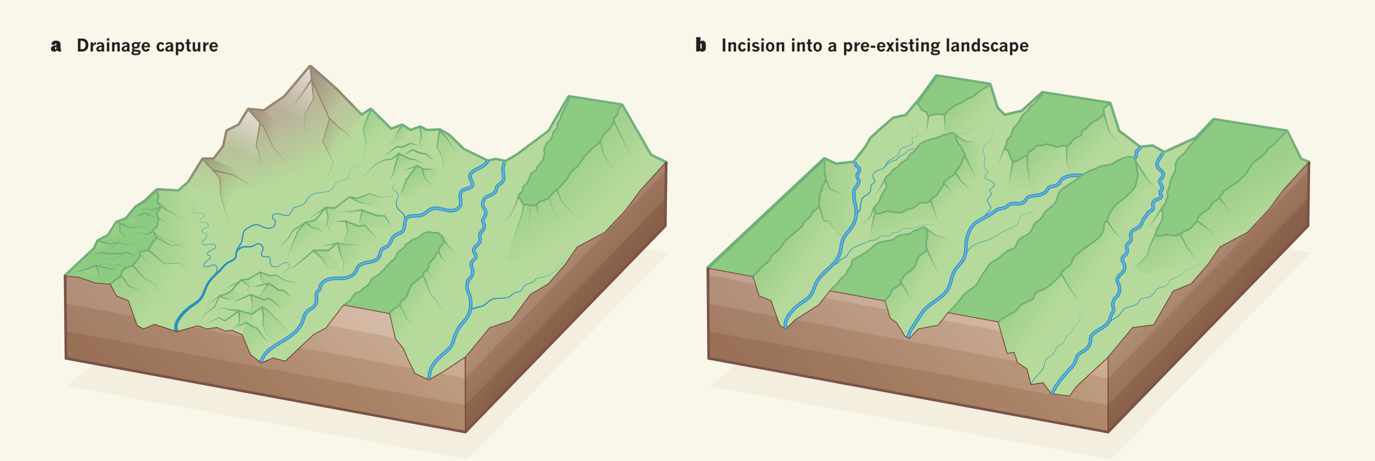

Figure 1 | Characteristics of low-gradient mountain terrain depend on the formation mechanism. Two mechanisms have been proposed for the formation of relatively flat surfaces in mountainous regions: drainage capture[2], which depends on the expansion and contraction of river networks during mountain building, and river incision into a pre-existing and slowly eroding low-gradient landscape[1]. **a**, Whipple *et al.*[3] report that surfaces formed by drainage capture will occur at different elevations, and become smoother at higher elevations. **b**, By contrast, surfaces formed by incision into a pre-existing landscape will be at approximately the same elevation, and will have low-gradient hill slopes and valleys that reflect the inherited topography.

deformation associated with the collision of the Indian continent with Asia[10]. Between these gorges are localized pockets of relatively flat surfaces, conventionally considered to be remnants of a part of the Tibetan Plateau that has been dissected by rivers for about 10 million years[4].

Yang *et al.* argued that the elevations of knickpoints (places at which steepening of the river channels occur) in this region are too scattered to reflect dissection of a common plateau, and that the relative gradients of river channels within and marginal to the flat surfaces imply the capture of one catchment by another. But Whipple and co-workers point out that the knickpoint elevations differ within a range of only about 500 metres, and that this could simply reflect the variability in elevations found on the original Tibetan Plateau. They also argue that evidence for capture of river networks is to be expected in the conventional dissection scenario, as a result of major rivers incising and expanding their valleys into the higher, pre-existing landscape.

Whipple *et al.* use numerical modelling to propose that surfaces formed solely by river capture should be characterized by: a random distribution in elevation (Fig. 1a); variable topographic relief that depends on the time elapsed since capture began; the presence of drainage divides at their margins that define the principally affected catchment area; and a reduction in relief at increased elevation (Fig. 1a), because the reduced erosional capacity of the victim's river system will cause a progressive increase in surface uplift in this region. The authors also propose that capture-formed surfaces will feature a remnant, high-relief rim at the upstream part of the catchment. However, such rims are unlikely to be ubiquitous in these surfaces, particularly if the initial reduction of erosion causes a positive feedback that drives capture across all of its bounding drainage divides. By contrast, remnant surfaces resulting from river incision into a pre-existing landscape should exhibit a relatively uniform elevation and relief that represents the topography of the original landscape (Fig. 1b).

Yang *et al.* reported that the observed variability of the scaling characteristics of river channels on low-gradient surfaces and channels marginal to those surfaces is another indicator of drainage capture. In their study, Whipple *et al.* spend little time considering this variability — presumably because these differences would also be a response to incision and expansion of valleys into a pre-existing surface.

The authors' list of diagnostic characteristics for surfaces generated by river capture compared with those generated by incision into a pre-existing low-gradient landscape presents a challenge to those who advocate the river-capture mechanism. An outstanding question is whether catchments that experience a reduction in drainage area have sufficient time to lower their hill-slope gradients before being fully captured and eradicated by the aggressively incising neighbour. Rates of erosion in the incised gorges of southeastern Tibet are of the order of 0.1–0.8 millimetres per year, but are much slower (about 0.02–0.03 mm yr^{-1}) on the remnant surfaces[4]. So the migration of drainage divides that is driven by trunk-stream incision must be substantially faster than the rate of lowering of hill slopes in the captured catchments.

Further testing is needed to determine the conditions under which captured catchments can lower their hill slopes sufficiently to mimic a low-gradient surface comparable to that resulting from incision into a pre-existing landscape. Whipple and colleagues' model of incision into a pre-existing Tibetan landscape also provides challenges, not least in working out how the surface remains relatively uniform across the region, despite the high degree of crustal strain advocated in some studies[2,10]. ■

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CORRECTION

The News & Views article 'Cancer genomics: spot the difference' by Noah D. Peyser and Jennifer R. Grandis (*Nature* **541,** 162–163; 2017) incorrectly stated that drugs that inhibit the activity of the protein KEAP1, which itself inhibits the transcription factor NRF2, could be used to combat activating mutations in the gene that encodes NRF2. Instead, it should have stated that this pathway could potentially be targeted for therapeutic use in certain oesophageal cancers if drugs are developed to inhibit mutant, activated NRF2.