death ligand 1 (PD-L1), which helps cancer cells to evade the immune system. The next step will be to establish whether LYTACs can also induce the degradation of multi-pass proteins that span the membrane several times, such as the ubiquitous G-protein-coupled receptors and proteins that transport materials across membranes (ion channels and solute-carrier proteins, for example). If so, it will be interesting to compare the performance of LYTACs, which would bind to the extracellular domains of such proteins, with that of PROTACs, which can bind to the intracellular domains of these proteins (as was recently demonstrated[6] for solute-carrier proteins).

As with any new drug modality, there is scope for improvement. For example, Banik and colleagues' first PD-L1-targeting LYTACs produced only partial degradation of the protein, which the authors attributed to low expression of CI-M6PR in the cell lines used. When the authors made a second type of LYTAC that incorporated a more potent PD-L1 antibody, degradation increased, albeit in cells that expressed greater levels of CI-M6PR than did the original cell lines. This shows that low abundance of the lysosome-shuttling receptor hijacked by the LYTAC (in this case, CI-M6PR) can reduce the effectiveness of these degraders. Similarly, the loss of core components of E3 ligases is a common mechanism by which cells become resistant to PROTACs[7]. Lysosome-shuttling receptors other than CI-M6PR could be used by LYTACs as alternatives, should resistance emerge. Degraders that target cell-type-specific receptors might also have improved safety profiles compared with conventional small-molecule therapeutics, which are not always cell-type selective.

What sets PROTACs and LYTACs apart from conventional drugs is their mode of action. For example, after a PROTAC has brought about the destruction of a target protein, the PROTAC is released and can induce further cycles of ubiquitin tagging and degradation, thereby acting as a catalyst at low concentrations[1,5]. Mechanistic studies are now warranted to determine whether LYTACs also work catalytically.

Another aspect of the mode of action of both PROTACs and LYTACs is that they bring two proteins together, to form a trimeric complex. A general feature of such processes is the hook effect, whereby trimer formation, and thereby the associated biological activity, decreases at high drug concentrations. This is because dimeric complexes generally form preferentially at high drug concentrations – an undesirable effect that can be alleviated by ensuring that all three components interact in such a way that trimer formation is more favourable than is dimer formation[1].

Kinetics also matters for protein degraders. For example, stable and long-lived trimeric complexes that involve PROTACs accelerate target degradation, improving drug potency and selectivity[8]. It will be crucial to understand how the complexes formed by LYTACs can be optimized to improve degradation activity.

PROTACs and LYTACs are larger molecules than conventional drugs. As a result of their size, PROTACs often do not permeate well through biological membranes, which can make them less potent drugs than the biologically active groups they contain. Size should be less of a problem for LYTACs because they do not need to cross the cell membrane, although they would still need to pass through biological barriers to combat diseases of the central nervous system. The development of lysosomal degraders that are smaller and less polar than LYTACs – and therefore more able to pass through membranes – will be eagerly anticipated. Small 'glue' molecules that bind to E3 ligases can already do the same job as PROTACs[9].

Targeted protein degradation is a promising therapeutic strategy, and the first PROTACs are currently in clinical trials[10]. LYTACs will need to play catch-up, but they have earned their place as a tool poised to expand the range of proteins that can be degraded. Their development as therapies will require an understanding of their behaviour in the human body – their pharmacokinetics, toxicity, and how they are metabolized, distributed and excreted, for example. It can be challenging to optimize the biological behaviour of molecules that incorporate large groups, such as antibodies and oligoglycopeptides, during drug discovery, but this problem can be overcome by further engineering the structures of these groups[11]. Banik and colleagues' new approach to degradation therefore warrants an all-hands-on deck approach.

Scientists working in drug discovery will eagerly await the development of LYTACs and the emergence of other methods for the drug-induced degradation of proteins[12]. Is no protein beyond the reach of degraders?

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This article was published online on 29 July 2020.

Ecology

Rethinking extinctions that arise from habitat loss

Joaquín Hortal & Ana M. C. Santos

Does the loss of species through habitat decline follow the same pattern whether the area lost is part of a large or a small habitat? An analysis sheds light on this long-running debate, with its implications for conservation strategies. **See p.238**

Understanding how habitat size affects the abundance of all the species living in a community provides ecological insights and is valuable for developing strategies to boost biodiversity. On page 238, Chase *et al.*[1] report results that might help to settle a long-running debate about the relationship between the area of a habitat and the diversity of species it can host.

Land transformation by human activity is a major component of global change. The loss of natural habitats reduces the local diversity and abundance of species[2], and has been implicated in more than one-third of animal extinctions worldwide between 1600 and 1992 (ref. 3). A report from the Intergovernmental Science-Policy Platform on Biodiversity and Ecosystem Services estimates that currently more than half a million species – about 9% of all terrestrial species – might lack the amount of habitat needed for their long-term survival[4]. Moreover, their disappearance would compromise many key ecosystem services, such as pollination or the control of pests or disease-causing agents.

The effect of habitat loss on biodiversity has

been conventionally estimated on the basis of the relationship between area and species richness, which was first described more than 150 years ago[5]. This seemingly universal relationship is simple: the larger a given habitat's area, the more species it holds, although the number of species increases with area in a nonlinear way[6]. There is a limit to the number of individuals of ecologically similar species that can persist in an area, owing to the limited resources that it harbours[7]. When a habitat loses part of its area, therefore, for many species, it also loses its capacity to support populations that are large enough to be viable. These species become extinct as habitat area diminishes with land-use intensification[8].

Chase and colleagues propose an elegant and simple approach to account for the dynamics of communities occupying habitat patches of different size. Rather than considering only the overall number of species in each habitat fragment, the authors focused on the number and relative abundance of different species in samples obtained from such fragments. This allows the structure of ecological communities to be compared directly[2], while avoiding problems that can arise when taking into account the differences in the effort needed to sample large and small areas[9]. The authors' approach also allows a comparison of variations in the relative abundance of individuals of all species, a measure of community structure that is associated with ecosystem dynamics[10].

Thanks to this method, Chase *et al.* could distinguish between three patterns of change that might occur as an outcome of habitat loss (Fig. 1). In the pattern described by the 'passive sampling' model, the structure of the community remains the same in large and small fragments. Therefore, each sample provides similar species richness (the number of species), abundance (the number of individuals) and evenness (the allocation of individuals to the different species), regardless of the total habitat size. In this case, species decline will mirror the loss of habitat area under the classical species–area theory[5], and the total number of species in the entire fragment would depend solely on its size.

The other two patterns are described as types of ecosystem decay – a hypothesis proposing that a habitat that shrinks undergoes a disproportionately high loss of organisms compared with the loss of habitat area. One type of ecosystem decay is proposed to occur owing to excessive loss of individuals. Smaller habitat fragments will contain fewer individuals per sample than will larger ones, and all species are equally affected. This generates communities with fewer species in smaller fragments, but no changes in the relative abundance of species per sample between small and large fragments.

The other type of ecosystem decay occurs owing to uneven changes in relative species abundances coupled to species loss. In this scenario, the species present have different responses to habitat loss, and therefore species become relatively more or less abundant in smaller fragments than in larger fragments. Their relative abundance becomes more uneven in samples from smaller fragments as some species increase their numerical dominance, impoverishing the community and causing it to become species poor.

Using data from around 120 human-transformed landscapes worldwide, Chase *et al.* show that, in general, samples from small fragments of natural habitat have fewer individuals, fewer species and a more uneven abundance of species than samples taken from larger fragments do. This outcome is consistent with a generalized pattern of ecosystem decay, mainly as a result of a decline in evenness (see Fig. 1), and this result holds, regardless of the type of habitat or organism studied. This implies that the alteration of natural habitats causes major functional changes in ecosystem dynamics that go beyond simply losing populations and species. Therefore, current estimates of extinctions associated with habitat loss made on the basis of the passive-sampling model might be underestimating not only the number of species that are threatened or already gone, but also the consequences of their loss for ecological functioning and the provision of ecosystem services.

Changes in biodiversity after habitat loss alter many ecological processes[11], eventually causing catastrophic effects that accelerate the extinction process[12]. But local extinctions are often not immediate. Some species persist with reduced abundances and declining population dynamics – known as 'extinction debt' – that lasts until the final individuals perish[13]. This causes an uneven distribution of species abundance that is vividly demonstrated by Chase and colleagues' method. Their analysis reveals a few 'winning' species that dominate the community in small habitats, and a very large number of rare species, many of which are probably heading towards extinction.

Declining species can be replaced by others coming from the neighbouring human-altered landscape, particularly in habitat edges[14], producing what are described as 'edge effects' that are comparatively more important in smaller fragments. Indeed, in the early stages of land transformation, communities in small fragments are more different from pristine communities than are those in large fragments, with communities in small fragments becoming more similar to those in large

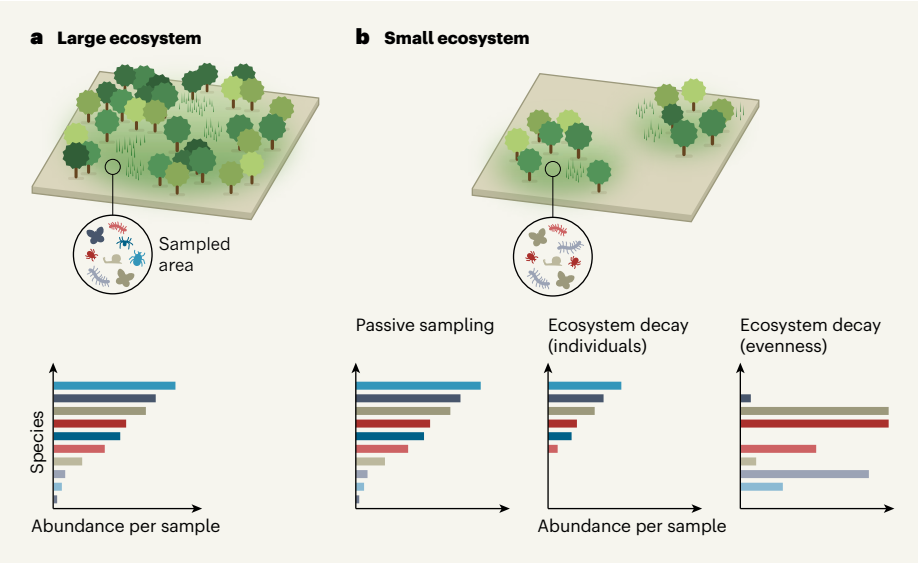

Figure 1 | Assessing how habitat size affects ecosystem dynamics. Understanding the relationship between a decline in habitat area and the effect on species is crucial for designing conservation strategies. **a**, **b**, Chase *et al.*[1] analysed studies that sampled species in particular habitats. The authors compared the diversity of organisms, such as insects, in samples obtained from large ecosystems (**a**) with samples taken from the same sampling area in a smaller fragments of the same type of habitat (**b**). These graphs show hypothetical results for species abundance per sample, and different species are shown in different colours. This method enabled the authors to distinguish between three possible outcomes as habitats become smaller. In the passive-sampling model, species are equally distributed in habitat fragments of any size, so the richness, abundance and relative species prevalence (evenness) per sample is constant, regardless of the total habitat size. In the ecosystem-decay (individuals) model, samples from smaller fragments have fewer individuals and species per sample than do samples from larger fragments, and all species abundances decline in a similar way as habitat is lost. In the ecosystem-decay (evenness) model, species vary in their response to habitat loss, and there is a change in their relative abundances. Chase *et al.* find that ecosystem decay, usually following the evenness model, is the best match for the observed data.

fragments over time, as they recover from the effect of land transformation[2]. According to Chase and colleagues, the degree of decay in diversity and species abundance found between large and small fragments is smaller in the older or 'softly' transformed European landscapes than in the more recently and dramatically transformed North American ones. This indicates that, over time, species moving in from the edges of the human-altered habitats might compensate, at least in part, for the ecological functions carried out by native species in larger habitats, causing small fragments to reach a new – yet different – ecological balance.

Although this work underscores the key role of habitat area in maintaining ecosystem processes, there is little exploration of how these processes are altered by habitat loss. Species from higher trophic levels (the upper levels of the food chain), such as predators, require larger areas to maintain their populations compared with species from lower trophic levels, so the number of individuals supported by smaller habitat fragments might not suffice to maintain populations of top predators or consumers, and hence would produce shorter food chains and alter the ecosystem structure[15]. Differences in extinction rates between trophic levels can cause striking changes in ecosystem functioning at habitat edges[16], jeopardizing the functioning and ecosystem-service provision as natural habitats diminish in size[11].

Chase and colleagues' results call for a reconsideration of the debate over whether a single large area devoted to conservation would preserve more species than would several small ones that combine to make up the same total size[17]. Some current evidence suggests that one continuous habitat might host fewer species than do many small patches that total the same area[18]. However, the large ecological changes that these small fragments might undergo could end up resulting in massive reductions in ecosystem function and, ultimately, increased extinction rates of native species over the long term compared with the case for a single, large protected area.

Chase and colleagues' approach is good for providing a general overview of the extent of these effects, but to understand exactly how ecological processes are changing locally, a higher level of detail will be needed. This will require going beyond the studies of trophic chains[14,16] to assess more-complex food webs[15], and to gather information on changes in species' functional responses and trait diversity in increasingly smaller habitats. Ultimately, this information will reveal which ecological processes are decaying, and what the consequences of such ecosystem decay are for the maintenance of fully functional biodiversity.

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This article was published online on 29 July 2020.

Mechanobiology

Stretch exercises for stem cells expand the skin

Matthias Rübsam & Carien M. Niessen

Stretching the skin of mice reveals that mechanical strain is communicated by a subpopulation of stem cells that proliferate and promote mechanical resistance, and so generate extra skin. **See p.268**

The cells of our bodies are exposed to a range of mechanical forces – including compression, shear and stretching – that they must resist to maintain tissue integrity and function. For example, skin responds to stretching forces by expanding. Physicians have exploited this particular response for more than 60 years[1], implanting stretching devices in the skin to cause tissue expansion for plastic surgery or to repair birth defects[2]. But exactly how mechanical strain creates extra tissue in a living organism has not been known. On page 268, Aragona *et al.*[3] now provide compelling insights (at the molecular, single-cell and cell-population level) into how stem cells in the skin of mice sense and communicate stretch to make new tissue.

The surface of the skin – a multi-layered tissue called the epidermis – protects organisms against dehydration and environmental stresses, including mechanical challenges. To ensure lifelong protection, the epidermis is constantly renewed through the generation of new stem cells in its basal layer. This renewal is balanced with differentiation and the movement of stem cells to generate the upper, barrier-forming layers of the epidermis. Ultimately, the barrier-forming cells are shed from the surface, to be replaced by new cells.

Aragona *et al.* set out to examine how the epidermis responds to strain. The group positioned a device used in human surgeries – a self-inflating gel – under the skin of mice. They then examined indicators of force perception, including changes in cell shape, the structure of a mechanosensitive protein called α-catenin, and a network of keratin proteins that provides cells with mechanical resilience. This analysis revealed that epidermal stem cells do indeed sense and respond to strain. The authors observed a temporary increase in stem-cell division, followed by thickening of the epidermis. Thus, increased stem-cell renewal fuels stem-cell differentiation. The two effects combine to maintain a functional barrier at the same time as extra skin is generated.

The researchers next genetically engineered cells in the basal epidermal layer such that the stem cells and their descendants were fluorescently marked. Tracking of these cell lineages over time confirmed that stretching tips the renewal–differentiation balance in favour of making more stem cells. This explains why the epidermis expands in response to stretching.