monoclonal antibodies, small molecule inhibitors, peptides, and antibodies conjugated to chemotherapy agents. Indeed, several clinical trials are already underway, looking at targeting Eph receptors in diseases such as ovarian cancer, non-small cell lung cancer and melanoma. However, more work is needed to understand the complexities of signalling redundancy and bidirectional ephrin–Eph signalling, to enable optimal therapeutic targeting of Eph receptors.

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How ocean acidification can benefit calcifiers

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Reduction in seawater pH due to rising levels of anthropogenic carbon dioxide (CO_2) in the world's oceans is a major force set to shape the future of marine ecosystems and the ecological services they provide [1,2]. In particular, ocean acidification is predicted to have a detrimental effect on the physiology of calcifying organisms [3]. Yet, the indirect effects of ocean acidification on calcifying organisms, which may counter or exacerbate direct effects, is uncertain. Using volcanic CO_2 vents, we tested the indirect effects of ocean acidification on a calcifying herbivore (gastropod) within the natural complexity of an ecological system. Contrary to predictions, the abundance of this calcifier was greater at vent sites (with near-future CO_2 levels). Furthermore, translocation experiments demonstrated that ocean acidification did not drive increases in gastropod abundance directly, but indirectly as a function of increased habitat and food (algal biomass). We conclude that the effect of ocean acidification on algae (primary producers) can have a strong, indirect positive influence on the abundance of some calcifying herbivores, which can overwhelm any direct negative effects. This finding points to the need to understand ecological processes that buffer the negative effects of environmental change.

It is widely documented that ocean acidification directly reduces the growth, survival and reproduction of many calcifying species under future elevated CO_2 conditions [2,3], with molluscs described as being particularly vulnerable [4]. This intuitively suggests that ocean acidification has negative ramifications for the persistence of calcifiers in future oceans, which in turn will have flow-on effects to the broader ecosystem. Such conclusions are, however, largely drawn from single-species studies and simplified experimental 'communities' that may not necessarily translate to natural populations and communities [5]. For instance, fuelled by increased carbon availability, increased plant growth (primary productivity) has the capacity to stimulate greater consumption by secondary producers, so that CO_2 indirectly acts as a resource (e.g. habitat and food) for herbivorous calcifiers. These positive effects might overwhelm the direct negative effects of physiological stress of ocean acidification.

We tested the indirect effects of ocean acidification by examining the relationships between food and habitat (algal turfs) and a highly-abundant, herbivorous calcifying gastropod (*Eatoniella mortoni*) within a complex ecological system (i.e. CO_2 vents in the southwest Pacific; Supplemental Information). The potential for these taxa to interact are known from mesocosm studies [6] but are yet to be examined in their natural context, where acclimated benthic communities are shaped by long-term exposure to elevated CO_2. At these vents, indirect effects were the primary driver of net ecological change. First, biomass of habitat-forming turf is greater at vent sites than control sites (mean ± SE: 2.66 ± 0.11 vs 1.16 ± 0.21 g per quadrat), which drives greater levels of net primary productivity or oxygen production (Figure 1A; Supplemental information). Second, this boost to habitat biomass is positively correlated with gastropod abundance, with more gastropods at vent sites than control sites (82 ± 8.6 vs. 35 ± 4.7 per quadrat). Analysis of these observational differences indicates that gastropod abundance responded more to differences in habitat rather than elevated CO_2 (Figure 1B, Supplemental information). To further test whether indirect effects of increased CO_2 (i.e. enhanced habitat biomass and primary productivity) were the key driver of gastropod abundance, we undertook reciprocal translocation experiments of algal turfs between and within vent and control sites. We found that gastropod abundance responds more to an increase in algal habitat (ANOVA: $F_{1,32} = 40.7$, $p < 0.001$) rather than elevated CO_2 ($F_{3,32} = 0.73$, $p = 0.553$), independently of origin or target location.

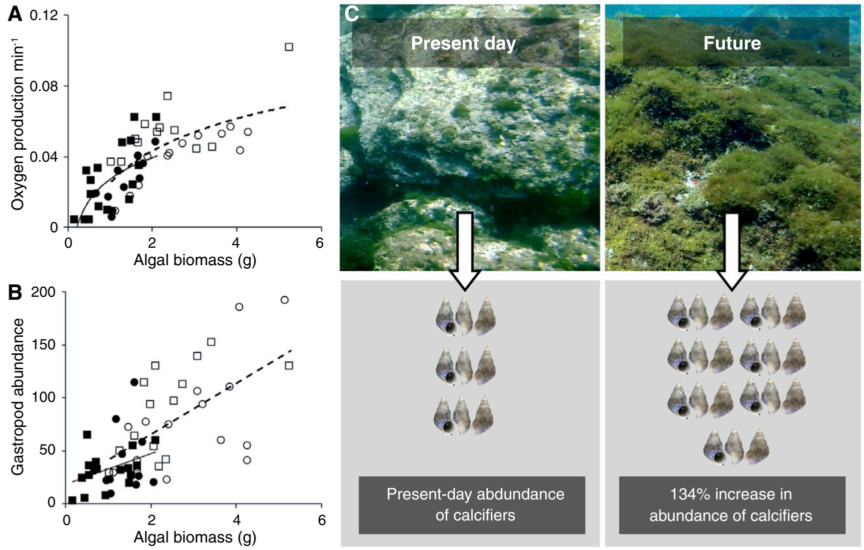

Figure 1. Response of a calcifying herbivore to future anthropogenic CO_2 enrichment within the natural complexity of their environment.

The response of (A) primary productivity ($F_{1,47}$ = 29.9, p < 0.001) and (B) gastropod abundance ($F_{1,53}$ = 21.4, p < 0.001) to increasing algal biomass (grams per quadrat) at two control sites (present-day CO_2 levels; black circles and squares) and two vent sites (future CO_2 levels; white circles and squares). Graph lines illustrate positive associations and images (C) illustrate present-day and future primary productivity and present-day and future gastropod abundance.

Our study demonstrates that primary productivity is greater at natural CO_2 vents and that this counterintuitively drove, via provision of more habitat and food, greater abundance of an herbivorous calcifier. This classic type of indirect effect suggests that whilst the direct effects of ocean acidification are readily detectable (e.g. survival, calcification, growth, development, and reproduction [3]), indirect effects of ocean acidification may leave a stronger imprint on species abundance. Therefore, not all calcifying organisms may undergo population decline, as predicted from small-scale laboratory and mesocosm experiments focussing only on direct effects [2]. Instead, some may undergo population increase. Indirect effects represent a suite of powerful mechanisms that shape the structure and functioning of ecological communities, but often result in surprising outcomes that cannot be predicted by investigating direct effects alone [7]. Whilst the indirect effects of ocean acidification on species interactions were initially surprising, we are only beginning to appreciate their ubiquity and strength [8,9]. We show how a vulnerable calcifier can benefit from elevated CO_2 and consequently thrive under physiologically stressful conditions (i.e. the increased energetic demands associated with acid-base regulation and building shell material) due to the counteracting role of increased food and habitat.

To date, most scientific thinking has focused on enriched CO_2 as a stressor by way of its associated reduction in aqueous pH. Whilst a stressor can be defined as an environmental disturbance that affects organisms negatively, it only captures one direction of biological response. Yet, as shown in this study, enriched CO_2 can act positively. Carbon enrichment acts as a direct resource for photosynthetic organisms [10]. Indirectly, therefore, increased CO_2 can act as a resource to consumers via the provision of food and habitat. Whilst ocean acidification has long been considered a stressor to calcifiers, this preoccupation tends to bound the range of responses we might anticipate (i.e. type and magnitude of negative response), thereby limiting our capacity to anticipate the factors that accelerate or stabilise against changes in ecological communities.

SUPPLEMENTAL INFORMATION

Supplemental information includes two tables, experimental procedures and author contributions and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2016.12.004.

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