Adaptation within natural variation

Artificial selection, also known as selective breeding, is a long-established method for exploring genetic variation and different adaptive phenotypes in a population. New experimental designs in evolutionary biology can combine this method with genetic sequencing to probe the mechanisms that underlie adaptive and evolutionary processes. With the growing availability of new sequencing techniques, researchers can now sequence multiple and diverse populations of organisms for a single study.

The evolve and resequencing (E&R) method is an increasingly popular study design that combines classic selection experiments with pooled genetic sequencing to quantify the genetic differences that accumulate after generations of selection. Mateusz Konczal (Jagiellonian University, Kraków, Poland) and colleagues recently used an E&R design to compare populations of wild-derived bank voles after artificially selecting one population for higher aerobic metabolic performance (*Mol. Biol. Evol.* doi:10.1093/molbev/msv038; published online 3 March 2015). After 13 generations, voles from selected lines achieved a 48% higher peak rate of oxygen consumption when swimming and showed a suite of other behavioral and physiological differences that distinguished them from a control population.

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Konczal's use of wild-derived voles sets this study apart from other E&R studies that frequently use model or domesticated lineages to explore genetic changes during artificial selection. While specific studies can benefit from controlled variation and the context of prior research, the inbred gene pools of model and domesticated lineages can limit the applicability of such studies to natural systems. "Our study differed from many other E&R studies (especially these performed on vertebrates) in the nature of the standing genetic variation available at the onset of the experiment," the authors noted, a characteristic they hoped would more closely model the dynamics of a natural vertebrate population.

Perhaps owing to this standing genetic variation, when Konczal's team sequenced each lineage of voles, they found very few differences in genes and allele frequencies between lines. Instead, they discovered, it was gene expression that differed. The authors identified 79 genes in the heart and 278 in the liver as differentially expressed between the two populations (no other organs were sampled). With very few genetic changes, short-term adaptation occurred largely within existing genetic variation through non-genetic changes, such as metabolic, hormonal and epigenetic modifications. "The results show that remarkable evolution of physiological performance can occur by regulatory changes within basically the same biochemical machinery," said Konczal in a press release. Where adaptation is concerned, these results also demonstrate the flexibility and resilience of a healthy and diverse gene pool in the face of strong selective pressures, artificial or otherwise.

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TO BOOST CANCER IMMUNOTHERAPY, JUST ADD OXYGEN?

Even when surrounded by immune cells, tumors often continue to grow. Their rapid growth consumes oxygen, leading to hypoxia in the surrounding area or tumor microenvironment. Hypoxia further promotes tumor growth by encouraging the release of adenosine, which prevents immune cells from entering the tumor microenvironment. Reducing this immunosuppression in the tumor microenvironment could free immune cells to attack tumors, boosting the efficacy of immune-based strategies for treating cancer.

Now, a research group led by Michail Sitkovsky (Northeastern University, Boston, MA) has shown how this can be accomplished. "Since the root of all problems is the lack of oxygen in tumors, a simple solution is to give tumors more oxygen," Sitkovsky told *NBC News*. His group evaluated how oxygen supplementation affected tumor growth and survival in mice with lung tumors. Mice that were placed in a chamber with a gas composition of 60% oxygen showed tumor regression and improved survival compared with mice breathing 21% oxygen, the composition of ambient air (*Sci. Transl. Med.* **7**, 277ra30; 2015). About 40% of tumor-bearing mice breathing 60% oxygen survived 60 days or more, whereas all the tumor-bearing mice breathing 21% oxygen died within 30 days. The anti-tumor effects of oxygen supplementation required the presence of two types of immune cell: T cells and natural killer cells. Hyperoxygenation seemed to inhibit the accumulation of adenosine, allowing the immune cells to infiltrate the tumor microenvironment and attack the tumor, which led to regression and long-term survival.

Supplemental oxygen therapy in cancer has produced mixed outcomes in previous studies. Earlier work using a higher concentration of oxygen (95%) showed toxicity and inflammation, and other reports indicated no benefit of oxygen supplementation, possibly due to a lack of immune cells. Sitkovsky's results indicate that immune cells are required for oxygen supplementation to bring about tumor regression.

Sitkovsky's group proposes that oxygen supplementation, either alone or in combination with immunotherapy, should undergo clinical testing as a cancer treatment but notes several limitations. The regression and survival outcomes observed in the studies required mice to be exposed to 60% oxygen on a continual basis, a requirement that could challenge patient compliance. Furthermore, although inhalation of 60% oxygen is not associated with toxicity and is considered safe in long-term treatments, it can exacerbate injury associated with ongoing acute lung inflammation and therefore should not be used during acute inflammatory episodes.

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