ETHICS WATCH

An Olympic tail?

A recent study showed that mice that received a gene transfer climbed faster and higher when weights were tied to their tails. Although this is unlikely to become an Olympic event, gene transfer has the potential to challenge our understanding of the meaning of excellence in physical achievement. So, has the day of the successful genetically engineered athlete dawned?

The drive for improvement is hardly new. Athletes in the ancient Olympics are said to have consumed a range of substances to enhance their abilities. Modern pharmacology entered sport with stimulants and anabolic steroids in the mid-twentieth century, and athletes have used biosynthetic drugs such as human growth hormone and, more recently, erythropoietin.

We know that gene transfer can produce the desired results in humans. A French study of patients with a lethal immunodeficiency showed that gene transfer boosted their immune systems. But we also know that it can have unpredictable and unwanted consequences — two of the patients subsequently developed leukaemia. Research with animals has shown that IGF-1 can prevent muscle wasting, so why not use it to build larger muscles? Injecting GHRH as naked DNA along with a regulatory sequence can increase weight and lean body mass — would-be American footballers might clamour for such a boost.

According to the renowned gene-transfer pioneer and Chair of the United States Recombinant DNA Advisory Committee, Ted Friedmann, the ingredients and skill for constructing such vectors are widely available.

With some athletes willing to try almost anything, with animal research showing performance enhancements, with the efficacy of gene transfer finally shown in humans and with the relative ease of vector assembly, how can anyone claim that the era of the "successful genetically engineered athlete" is not upon us? The answer lies in the modifier 'successful'.

Consider the relative crudeness of the technology, the complexity of gene action, and what makes an Olympic champion. Most gene-transfer techniques are the equivalent of blasting a genome with a shotgun — some of the pellets pass through, some land harmlessly and ineffectually, some cause damage and a fortunate few find a useful home in the genome.

Even when genes 'land well', we might face unanticipated and undesired consequences. For example, giving mice extra copies of the NMDA receptor made them experts at maze learning but more sensitive to pain. One factor distinguishing the frontrunners from the rest of the crowd is the ability to endure suffering, so a genetic manipulation that increased sensitivity would hardly be advantageous.

Are such unintended consequences competitive boosts or impediments? In truth, I do not know. But remember what it takes to become an Olympic champion — raw physical talent is necessary, but also focus, dedication, willingness to suffer for a desired end, attentiveness, competitive savvy, the ability to train intensely and recover rapidly, and a host of other natural talents and practiced virtues. Might gene transfer alter those 'natural' talents? Yes, it might. Would it assure success in the competition? Hardly. The methods are too crude, and the results too unpredictable in light of the multitude of factors that mold a champion.

So, will athletes and scientists conspire to try? Almost certainly. But this brings us to the familiar theme of immoral human experimentation, which is a threat to be sure, but not to the Olympics — at least not yet.

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TECHNOLOGY

Topped and tailed

Topping and tailing vegetables gets rid of their unpalatable ends, and now it seems that an analogous way of delivering RNAi provides a more digestible means of knocking down mammalian genes in a tissue-specific fashion.

Toshie Shinagawa and Shunsuke Ishii have come up with a new method of delivering long double-stranded RNA (dsRNA) to mammalian cells that avoids the interferon response, which is a viral defence mechanism that causes non-specific RNA degradation and cell death. Until now, the main problem with using an RNA polymerase II (Pol II) promoter in a vector for delivering RNAi was that Pol II transcripts are transferred from the nucleus to the cytosol, where they provoke the interferon response.

Shinagawa and Ishii circumvented this problem by constructing a vector — pDECAP — that expresses mRNAs that lack the 5′ 7-methylguanosine (m^7G) cap (the 'top') and the 3′ poly(A) tail that are required for transport to the cytosol. The ingenious addition of a ribozyme cassette ensures the m^7G caps are cut-off, whereas the omission of a poly(A) addition sequence effectively 'tails' the dsRNA transcripts.

So, topping and tailing the dsRNA blocks its export to the cytosol. It is only after the long dsRNA is processed into siRNA in the nucleus that it moves to the cytoplasm, where it degrades the target mRNA.

Using this strategy, the authors knocked down expression of the *Ski* oncogene in mice. They were able to effectively mimic the phenotype of *Ski*-knockout mice without the time-consuming process that the generation of such knockouts entails.

The big pay off from using this new strategy is that we are no longer limited to using promoters for RNAi vectors, such as Pol III, which are equally active in all cell types. By contrast, the Pol II promoter that transcribes all protein-coding genes in mammals can be made tissue-specific or inducible depending on interactions with various transcriptional regulators. So, this new approach allows easy and efficient generation of tissue-specific or inducible knockdown mice.

Doubtless RNAi transgenic systems that use small hairpin-type RNAs will retain their popularity in the near future, however, this new dsRNA strategy certainly represents a significant challenge to their dominance.

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References and links

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FURTHER READING McManus, M. T. & Sharp, P. A. Gene silencing in mammals by small interfering RNAs. *Nature Rev. Genet*. **3**, 737–747 (2002)

WEB SITE

Shunsuke Ishii's laboratory: http://www.riken.go.jp/engn/r-world/research/lab/wako/genetics/index.html