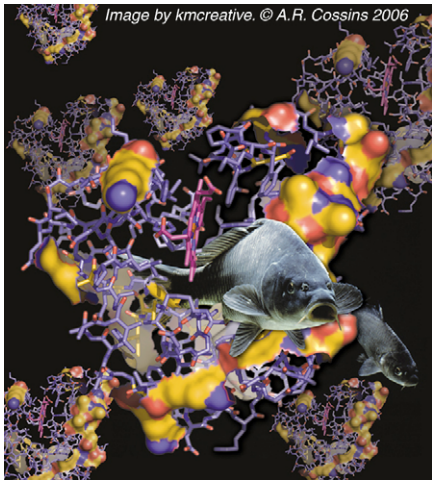
Inside JEB is a twice monthly feature, which highlights the key developments in the *Journal of Experimental Biology*. Written by science journalists, the short reports give the inside view of the science in JEB.

Inside JEB

PHENOTYPIC PLASTICITY



Anyone training for a marathon knows that although the goal may at first seem unattainable, with the correct exercise regime, even the least promising athlete will eventually cross the finish line. This remarkable phenotypic plasticity, which allows us to reshape our bodies within the strictures of our genetic make-up, has fascinated scientists for the last 3 decades. However, Hans Hoppeler explains that science didn't fully appreciate the value of phenotypic plasticity until the late 1960s; 'at that time scientists accepted that the physiology of the human body was something that was more or less genetically determined' he says. The phenotypic plasticity revolution began when scientists realised that a person's physical performance could be improved simply by physical training. Exercised muscles responded to the stimulation, and remodelled to improve performance. In the intervening years, scientists have characterised many physiological aspects of this phenomenon across a range of tissues, and with the advent of modern molecular tools, it has proved possible to uncover some of the mechanisms that underpin the phenomenon.

Given our increasing understanding of phenotypic plasticity at both the physiological and molecular levels, it was clear to Hoppeler that the time was right to assemble a comprehensive collection of review papers discussing recent progress in the field. Hoppeler, Martin Flück, Ken Lukowiak and Ted Garland teamed up to edit this selection of reviews discussing many aspects of phenotypic plasticity from the physiological effects in various tissues, through to the mechanisms that regulate it, culminating in the role of phenotypic plasticity in evolution.

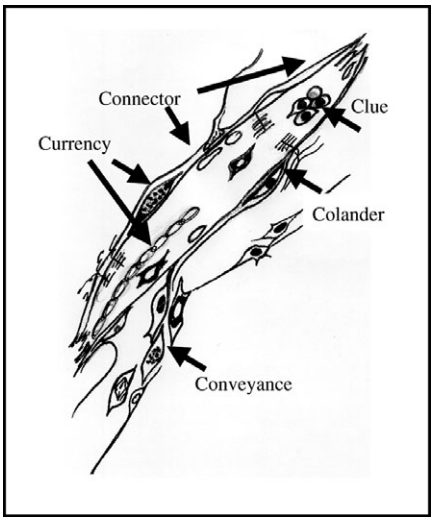
PHENOTYPIC PLASTICITY IN SKELETAL MUSCLE

The collection is opened by Martin Flück's discussion (p. 2239) of phenotypic plasticity of mammalian muscle, specifically in response to exercise. Outlining the physiological responses at the cellular level, Flück goes on to describe the characterisation of these responses to repeated short bouts of training over several weeks, as well as discussing stimuli, such as hypoxia, that may trigger metabolic adjustments in muscles in response to exercise.

Following on from Flück's overview of plasticity in mammalian muscle, Ian Johnston considers fish muscle and environmental effects during development. Johnston (p. 2249) describes how plasticity in the early stages of muscle development tends to be irreversible as larval development is so rapid. He adds that environmental influences on development can potentially affect the chances of later survival. However, during adulthood, Johnston discusses how a plethora of environmental and seasonal factors influence muscle phenotypes. Looking at adult fish from several species, including sculpins, the common carp and goldfish, Johnston outlines the effects that various factors have on muscle development, emphasising the lessons that we can learn about muscle phenotypic plasticity from model fish species such as *Danio rerio*.

Moving on from studies in the whole organism to take a look at the molecular mechanisms involved, David Hood and colleagues (p. 2265) describe the marked proliferation of muscle mitochondrial content that is triggered by exercise. Outlining the signals that trigger the expression and import of mitochondrial proteins into the organelle, the transcriptional activation of the 13 genes encoded by the mitochondrial DNA and alterations in the balance between mitochondrial fusion and fission required to increase the number of organelles in the tissue, Hood shows that all of these cellular events are highly coordinated. He adds that 'impairment at any step can lead to… an inability to maintain energy homeostasis'.

While conventional cell signalling events are essential for many aspects of muscle phenotypic plasticity, Judy Anderson from the University of Winnipeg, Canada, points out that stem-cell like satellite cells are also necessary components of muscle phenotypic plasticity (p. 2276). Anderson explains how satellite cells fulfil five main functions in muscle adaptation to environmental stimuli. Describing satellite



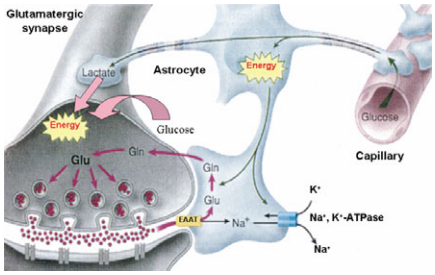
cells as the ‘currency’ of muscle regeneration, Anderson explains how satellite cell progeny nuclei fuse with muscle fibres, bringing with them a universal developmental program that drives muscle growth throughout ontogeny. She also outlines some of the other roles that satellite cells play in muscle phenotypic plasticity, and explains how satellite cell functions contribute to the phenotypic plasticity of muscle.

PHENOTYPIC PLASTICITY OF THE BRAIN

Although the effects of phenotypic plasticity in muscle can be physically dramatic, the effects in the brain, although less visible, are no less spectacular. Brains constantly remodel in response to a relentless barrage of physiological and environmental factors, allowing us to encode information by remodelling synaptic interactions.

Many different strategies have been used to uncover the underlying principles of phenotypic plasticity in memory formation, and studies of synaptic plasticity in memory formation in transgenic mice have proven to be highly effective in determining the neurobiology of learning and memory. But Peter Nguyen, from the University of Alberta School of Medicine explains that transgenic mice are developed predominantly from two strains of inbred laboratory mice, and that some inbred mice naturally exhibit memory problems that can ‘confound the interpretation of cellular neurophysiological phenotypes of mutant mice’ says Nguyen. Describing the methods involved in phenotyping hippocampal synapses in inbred mouse strains, Nguyen discusses how long-term memory formation is correlated with a form of long-term synaptic plasticity, known as long-term potentiation, and that it might be possible to identify cellular models in inbred strains that could be used to identify the mechanisms of memory impairment (p. 2293). By characterising synaptic plasticity in inbred mouse strains, Nguyen is optimistic that this information could be used to generate databases of memory impairment physiology that could be used in concert with genetic databases to design better models of memory impairment.

According to Pierre Magistretti, the brain consumes 20% of the entire body’s glucose and oxygen budgets. With such disproportionately high energy demands, the brain has developed an efficient astrocyte (a type of glia) system that takes up glucose, in turn delivering lactate to fuel synaptic transmission. This is known as the astrocyte–neuron lactate shuttle. Having identified this mechanism in the early 1990s, Magistretti and his team went on to find that ‘in addition, this neuron–glia metabolic coupling undergoes plastic adaptations in parallel to adaptive mechanisms that characterize synaptic plasticity’ he says. Magistretti explains that some neurotransmitters, such as adenosine and noradrenaline, appear to regulate the expression of key proteins involved in glycogen metabolism in response to synaptic activity, and by mapping brain activity has found that the metabolic demands of regions of the brain associated with learning and the sleep–waking cycle are extremely plastic (p. 2304).



Moving the discussion on from plasticity at the level of single synapses to plasticity in neural networks, Michael Colicos and Naweed Syed describe some innovative approaches to monitor the activities of large neuronal networks non-invasively by interfacing them with silicon devices (p. 2312). Giving us a brief chronology of the use of field-effect transistors through to recent developments in direct contact electronics, Syed describes his latest achievement with his collaborator Peter Fromherz, where they cultured *Lymnaea* neurones on a silicon chip to form an excitatory synapse that the team were able to modulate directly with the chip, ‘essentially creating a biological neural memory on a silicon chip’ says Syed.

MOLECULAR MECHANISMS OF PHENOTYPIC PLASTICITY

Many species exploit phenotypic plasticity to adapt to changing environmental conditions, but phenotypic plasticity also gives us the flexibility to adjust to a wide range of physiological influences such as toxic environments and physiological stressors. One tissue that responds strongly to a variety of physiological strains is the human heart; heart disease, in response to hypertension and mechanical overloading, is one of the largest killers in western society. Having outlined the initial events that trigger myocardiac remodelling in heart disease, Bernard Swynghedauw also discusses the mechanosensory mechanisms that activate the transcription factors regulating cardiac remodelling (p. 2320). According to Swynghedauw, cardiac remodelling involves the reactivation of the foetal development program, as well as triggering fibrosis and apoptotic cell death through coordinated changes in over 1,400 genes.

While the human heart remodels in response to various disease states, other species, such as fish, adapt their physiology as they experience routine seasonal climate fluctuations. For example, poikilothermic carp are able to tolerate temperatures ranging from less than 4°C to almost 40°C. Curious to know whether carp tissues benefited from a single stress response to cold exposure, Andy Cossins and his team in Liverpool, UK, designed a cDNA microarray containing approximately 14,000 clones to identify genes involved in the cold stress response (p. 2328). Having exposed carp to temperatures ranging from 10 to 23°C for 21 days, the team collected samples from seven tissues, including intestine and muscle, and found a common stress response that included the increased production of gene transcripts for stress proteins and factors associated with protein and ATP turnover. The team also identified several responses that were tissue specific, such as the upregulation of transport genes in the intestine, while cell motility genes were significantly downregulated in muscle. Cossins adds ‘we have identified a large number of candidate gene targets with which to investigate adaptive responses to environmental change’.

Changing scale from plasticity in tissues to plasticity at the cellular level, Chris Goldring describes a multitude of cellular responses to pathogenic and chemical challenges (p. 2337). According to Goldring and his colleagues ‘there exists a

large degree of plasticity in the innate ability of a cell to defend itself… at multiple layers' and adds that 'the control of transcription is fundamental to this process'. Goldring outlines a number of molecular techniques that have been used to identify redox-sensitive transcription factors involved in cellular protection against chemical injury and bacterial infection, such as NF-κB. Focusing on the liver as a model organ that has evolved a suite of adaptations to resist chemical damage, Goldring discusses the role of another transcription factor, Nrf2, in protecting liver cells from injury.

THE ROLE OF PHENOTYPIC PLASTICITY IN EVOLUTION

Having discussed phenotypic plasticity at the levels of cells, tissues and whole organisms, phenotypic plasticity can also be considered as 'the ability of one genotype to produce more than one phenotype when exposed to different environments' explains Ted Garland (p. 2344). After introducing the concept of phenotypic plasticity from an ecological and evolutionary perspective, Garland and Scott Kelly go on to provide examples in both vertebrates and invertebrates of selective breeding programs under various environmental pressures that have been used to investigate the evolution of plasticity in mice and *Drosophilia*. Garland points out that directional selection, where individuals with higher values of a certain trait are favoured by selection, would seem to benefit individuals with greater phenotypic plasticity and lead to increased plasticity across the generations. Although this is certainly the case in many situations, such as flies raised on a lemon diet that demonstrated enhanced detoxifying enzyme plasticity, Garland reminds us of the possibility that selective pressure could also reduce phenotypic plasticity on occasions when the trait had already evolved close to some 'ceiling value'.

Progressing on from Garland's discussion of the evolution of phenotypic plasticity in response to selection, Massimo Pigliucci discusses the next logical progression 'Genetic Assimilation', where a plastic response begins to be expressed constitutively in the absence of the original environmental signal (p. 2362). However, Pigliucci explains that the concept of genetic assimilation has recently come under attack. Outlining the arguments that have been raised against genetic assimilation, Pigliucci, Courtney Murren and Carl Schlichting recount the misunderstandings that have arisen and explain that 'phenotypic plasticity is a developmental *process*, not an evolutionary one' and as such could 'be the target of natural selection… [yielding] the evolutionary *outcome* of genetic assimilation or phenotypic accommodation'.


Photo courtesy of Geoffrey E. Hill and David Bay

Trevor Price's review considers colour patterns in birds, which are plastic in response to various environmental factors and also subject to both natural and sexual selection (p. 2368). Explaining that birds use elaborate plumage colouring for communication, Price points out that colouring should also 'evolve to be phenotypically plastic indicators of an individual's quality'. Price explains that varying the levels of carotenoids in bird diets produces changes in the bird's colouring, which is thought to have 'altered the phenotype, driving genetic evolution in novel directions' he says. Having discussed the role of phenotypic plasticity in driving genetic change, Price points out that other mechanisms, such as spontaneous mutations in the genome, can also bring about genetic change.

Concluding the section of papers discussing phenotypic plasticity in evolution, James Fordyce from the University of Tennessee, USA, discusses the evolutionary consequences of interspecies interactions mediated through phenotypic plasticity (p. 2377). Illustrating his discussion with copious examples of ecological interactions, Fordyce discusses 'predictable phenotypic plasticity', where the response of one species to another's influence in turn modifies the response of the second species to the first. An example of this form of plasticity is found when plants defend themselves against browsing herbivores, which are themselves selected on the basis of their tolerance to the plants' defence mechanisms. Phenotypic plasticity can also vary through a population in time and space, as well as affecting the strength of evolution when the interaction of one species with another is in turn affected by the phenotypic plasticity of the other species.

PHENOTYPIC PLASTICITY AND THE FUTURE

This collection of 14 review articles takes us through many levels of phenotypic plasticity in biological systems and some of the powerful new tools that will eventually unlock the fundamental principles underpinning the phenomenon. There are clearly many more aspects of phenotypic plasticity that have yet to be investigated, but having established the current state of our understanding of phenotypic plasticity, Hoppeler is optimistic that the coming decade will reveal many of the mechanisms that have so far eluded us.

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