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NEWS AND VIEWS

PERSPECTIVE

Xmrks the spot: life history tradeoffs, sexual selection and the evolutionary ecology of oncogenesis

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In a classic paper, George Williams (1957) argued that alleles promoting reproductive success early in life may be favoured by selection, even if they reduce the lifespan of individuals that bear the allele. A variety of evidence supports the theory that such 'antagonistic pleiotropy' is a major factor contributing to the evolution of senescence (Ljubuncic & Reznick 2009), but examples of specific alleles known to fulfil Williams' criteria remain rare, in both humans and other animals (e.g. Alexander *et al.* 2007; Kulminski *et al.* 2010). An intriguing example in this issue of *Molecular Ecology* (Fernandez & Bowser 2010) demonstrates that both natural and sexual selection may favour melanoma-promoting oncogene alleles in the fish genus *Xiphophorus*.

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Antagonistic pleiotropy is expected under natural selection but may become even more pronounced under sexual selection. Trivers (1972) emphasized that sexual selection will often favour different life history tradeoffs (and hence mortality rates) for males and females. The potentially high advantage of success in competition for mates for males means that traits conferring a significant reproductive advantage early in life but imposing increased mortality later will frequently be favoured in the balance between sexual selection and natural selection, leading to shorter lifespan in males than females. Such sexually-selected traits are less likely to be favoured in females, where the reproductive rewards of successful competition for mates are typically lower. Nevertheless, females may evolve to prefer traits in males that will contribute to an early demise for their sons, if the advantage of their early reproductive success is sufficiently strong (Kokko *et al.* 2002).

Enter the swordtails and platyfishes (genus *Xiphophorus*). These fish are well-known to evolutionary biologists as premier subjects of research on sexual selection, including mate choice, aggression, competition for mates and alternative strategies (e.g. Ryan *et al.* 1990). Less well known is the role of these fish as models for analysing carcinogenesis. Experiments in the 1920s demonstrated that hybrids between platyfishes and swordtails showed a striking propensity to develop malignant pigment-cell tumours – melanomas—among the most deadly cancers of humans. Research since has revealed that melanomas develop within species as well as in hybrids, which has led to *Xiphophorus* becoming a model system for studies on the molecular biology and genetics of melanoma (MeierJohann & Schartl 2006).

The major gene underlying melanoma formation, *Xiphophorus* melanoma receptor kinase (*Xmrk*) was identified by Wittbrodt *et al.* (1989). This sort of gene is of special interest to cancer biologists, given a central role for high activity of such tyrosine kinases in progression of diverse forms of human cancer. In *Xiphophorus*, runaway tyrosine kinase activity, due to high expression of *Xmrk*, leads to development of a large black spot on the fish's side—a cancer that destroys muscle, reduces swimming speed and causes early death (Fig. 1). Despite such deleterious effects, the oncogenic *Xmrk* allele persists in some natural populations of *Xiphophorus*, suggesting the presence of benefits early in life that outweigh late costs—the hallmarks of antagonistic pleiotropy.

In this issue of *Molecular Ecology*, Fernandez & Bowser (2010) investigate the expression of *Xmrk*, the spotted caudal (Sc) phenotype (the pigment pattern that expresses *Xmrk*) and melanoma in the context of body size in *Xiphophorus cortezi*. The Sc phenotype shows incomplete penetrance and hence fish carrying *Xmrk* may not express the spotted caudal pattern. Body size is known from previous

Fig. 1 *Xiphophorus cortezi* with the exaggerated Sc phenotype caused by the *Xmrk* oncogene. Photo by A. Fernandez.

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research to be strongly predictive of reproductive success in a number of species of *Xiphophorus*, so a positive association of *Xmrk* with body size would fit the pattern predicted by Williams: a gene promoting reproductive success early in life but with a cost later on. Since larger body size increases reproductive success in *Xiphophorus* through mate choice and competition for mates, sexual selection is likely involved as well.

Fernandez & Bowser (2010) set out to investigate several key properties of this system. First, is the *Xmrk* gene common and widely distributed among populations? Second, does melanoma occur even when there is no opportunity for hybridization? Third, is there a sex-bias in the occurrence of *Xmrk* and of melanoma? And finally, are the *Xmrk* gene and melanoma correlated with a key life history feature, large body size, in these fish?

The authors collected fish from four localities in Mexico, spanning the range of *X. cortezi*, one of which, Arroyo Conchita, contained only this species, precluding the possibility that ongoing hybridization sustains the oncogenic *Xmrk* allele. They measured standard length for all individuals sampled and collected tissue for genetic analyses. Cloned sequences of the *Xmrk* gene from a closely-related species of *Xiphophorus* were used to design primers that allowed them to amplify both the *Xmrk* oncogene and a closely related proto-oncogene (a gene that when mutated, can become oncogenic). They also carried out detailed histological sampling of nine individuals (eight male, one female) from Arroyo Conchita, that appeared to have abnormal melanophore phenotypes on visual inspection. They analysed the data on males and females separately to investigate associations between the presence of the *Xmrk* genotype, the Sc phenotype, melanoma and body size.

Their results, in combination with those of previous studies, demonstrate that the *Xmrk* polymorphism is widespread throughout the range of *X. cortezi*. There was a pronounced sex bias in favour of males (replicating results from other populations and species), but both sexes showed high frequencies of the *Xmrk* genotype in some populations, with a maximum of 82% for males and 57% for females in the Arroyo Conchita population. The study definitively confirms that non-hybrid *Xiphophorus* develop melanomas in natural populations, as the Arroyo Conchita population shows a high frequency of *Xmrk* and melanoma. For both males and females, individuals carrying the *Xmrk* allele were significantly longer. For males, this difference was not associated with the Sc phenotype, whereas there was a marginally significant association for females. Finally, males with melanoma (and *Xmrk*) were significantly longer than both males with *Xmrk* but without melanoma and males without *Xmrk* (melanoma was not found in males without *Xmrk*).

The authors argue convincingly that both natural and sexual selection likely contribute to the high frequencies of *Xmrk* in natural populations. Large size thus provides a variety of advantages to both males and females in the context of natural selection, including increased access to resources and protection from predation. For females, substantial gains in fecundity would also be associated with increases in size.

Previous research has demonstrated that for many species of fish, including a variety of species of *Xiphophorus*, large size confers advantages to males in terms of attractiveness to females and success in competition for mates. Further evidence for the efficacy of sexual selection on the frequency of *Xmrk* comes from earlier studies by the first author. In a recent paper (Fernandez & Morris 2008), mate choice experiments were used to demonstrate that female *X. cortezi* prefer males with the Sc phenotype that is associated with *Xmrk*. Another study (Fernandez 2010) demonstrated a significant positive association between the *Xmrk* genotype and aggression in males, which engenders success in competition for mates. Hence the high frequency of *Xmrk* in males, relative to females, makes sense given the strength of sexual selection.

This research provides an outstanding example of antagonistic pleiotropy, in which the allele exhibiting the pleiotropic effects has been identified. It should now be possible to test the hypothesis that the benefits of the oncogenic *Xmrk* genotype outweigh its costs and how the benefit to cost ratio varies with the frequency of *Xmrk*. Intriguingly, Fernandez & Morris (2008) showed that in one population with a particularly high frequency of *Xmrk*, females preferred males without the Sc phenotype. Hence when *Xmrk* reaches high frequencies, negative effects such as the production of offspring with two copies of the *Xmrk* gene (which have low viability) may override the advantages associated with increased aggressiveness, attractiveness and large size (Fernandez & Morris 2008).

The authors offer several tantalizing insights into possible mechanistic connections between *Xmrk* and cancer. The *Xmrk* oncogene is derived via duplication from an epidermal growth factor receptor and hence may mediate both normal and abnormal growth through interactions with growth factors such as IGF-1. This type of interaction, involving constitutive over-expression of growth-related genes, is central to the development of numerous cancers in both humans and non-human animals (e.g. Hankinson *et al*. 1998). Further, *Xmrk* is near (and likely linked to) pigment production genes like *Mc1r* that are overexpressed in melanoma. Finally, previous work (Fernandez 2010) demonstrating a link between *Xmrk* and aggression suggests a role for androgen expression—and high androgen levels are associated with tumour formation in both humans and other animals (Summers & Crespi 2008).

Previous studies have connected greater height with increased human cancer risk, an observation that motivated the interests of Fernandez & Bowser (2010) in this phenotype for *Xiphophorus*. Recent studies have also identified candidate genes in humans that may mediate antagonistic pleiotropy, associated, as in *Xiphophorus*, with selection for enhanced growth due to sexually-selected or other benefits early in life, at the expense of later increased risk of cancer. Thus, polymorphisms in the High Mobility Group At-hook 2 (HMGA2) gene influence height in humans (Yang *et al*. 2010), HMGA2 variants with high levels of expression are

associated with increased risk of cancer and poor prognosis (Young & Narita 2007) and a series of papers has demonstrated higher reproductive success of taller men (Sear 2006). Replicated associations between higher birth weight and increased risk of breast and prostate cancer in humans (Cnattingius *et al*. 2009; Oberg *et al*. 2009) hint at a broad swath of antagonistically pleiotropic effects in human cancer risk and high relevance of *Xiphophorus* as a model system for the genetic basis of human polygenic disease.

This paper validates a tractable system for investigating antagonistic pleiotropy in natural populations, which allows intensive investigation, from gene to natural population, of the mechanisms that connect reproductively advantageous traits, such as large size, to traits that increase mortality in adults, such as cancer. More generally, a new empirical field has been born, the molecular evolutionary ecology of cancer, which should stimulate similarly-novel studies that dissect the forces of selection that hold us and other animals, delicately poised at some mark between sex and death.

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