Myosin – a monarch of pigment transport?

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Animals, from insects to mammals, use colouration for a variety of functions including camouflage, photo-protection and seduction of a mate. However, with the exception of well-studied model organisms, such as the mouse, relatively little is known of the molecular basis of colouration and the variation between individuals within a species. Now, an interesting genomic study of the monarch butterfly (Danaus plexippus) published in Nature raises the possibility that a common myosin-Va-dependent protein trafficking pathway could regulate colouration by different pigments in different pigmented structures in distantly related species.

The monarch butterfly lays its eggs on the leaves of milkweed plants, from which its caterpillars ingest cardiac glycosides. These accumulate at toxic levels within the caterpillar and adult butterfly. To warn predators of this danger, monarchs display bright orange wing colouration. Interestingly, the monarch population of the Hawaiian Island Oahu is polymorphic for wing colouration and a white morph known as ‘nivosus’ has been observed there since the 1890s. Classical genetic experiments revealed that the white allele segregates as a single autosomal locus and is recessive to the wild type, meaning that it is maintained at a low frequency (<1%) within the population. In view of the reduced pigmentation, it had been generally considered that the nivosus phenotype most likely results from defects in the biosynthesis of the orange pigment that colours the wildtype monarch wing. However, based on their data, Zhan et al. raise the possibility that pigment transport, rather than production, might be to blame for the white wing colour of nivosus.

To investigate the molecular basis of the nivosus phenotype, Zhan and colleagues sequenced the genomes of 12 Hawaiian monarchs, five white and seven orange wild-type individuals, three of which were first- or second-generation descendants of white monarchs. They then scanned SNP genotypes within the genomic data set (and that of 101 other monarchs from around the world, whose genomes were sequenced as part of a large-scale study aimed at identifying genes linked to the migratory behaviour of North American monarchs published in the same study) for segregation patterns that matched the Mendelian inheritance pattern of the nivosus phenotype. This analysis reports markers in a single gene, DPOGS206617 (sequence available at http://monarchbase.umassmed.edu/tools3/Get_gene.cgi?id=DPOGS206617), that segregate with the white phenotype. In their report, Zhan et al. indicate that this gene encodes a myosin motor protein and suggest that this putative myosin might function in a similar fashion to mammalian myosin-Va in pigment organelle transport in pigment cells (melanosomes in melanocytes).

Myosin-Va is a type V alternative myosin (equivalent to type IX in plants), and this class of highly conserved myosin plays important roles in intracellular transport of organelles (such as melanosomes), mRNA and other cargo (Hammmer and Sellers, 2012; Trybus, 2008). In common with other myosins, myosin-V heavy chain contains three hallmark domains (from the N-terminus); a motor/head domain that binds and hydrolyses ATP and allows reversible association with F-actin tracks, a neck domain/lever arm which binds to light chains/calcmodulin and amplifies the small ATPase-dependent conformation changes in the motor domain to generate the power-stroke, and a tail domain that allows cargo binding. Typically type V myosins have adaptations to these core domains that facilitate their role as transporters. Firstly, the tail domain contains a series of amphipathic alpha-helices that allow dimerization of the heavy chains. Secondly, the motor domain has a high duty ratio, that is it spends ~80% of the ATPase cycle in high affinity contact with F-actin, meaning that it does not diffuse away from the actin track. Finally, the lever arm is extended and comprises six IQ motifs that can bind three calmodulin light chains and allow the myosin-V dimer to span the 36 nm helical pitch of F-actin. These adaptations allow myosin-V to walk hand-over-hand along actin filaments and thus drag cargo through the cytoplasm. In melanocytes, the tail of myosin-Va also allows its attachment to the melanosome membrane, via interaction with the small GTPase Rab27a and its effector melanophilin, and regulates the transport of melanosomes along F-actin into peripheral cytoplasmic extensions known as dendrites (Evans et al., 2014). Melanosome accumulation in dendrites is essential for their subsequent transfer to keratinocytes and thus skin and hair pigmentation. Consistent with this, mutations in the MYOVA gene (as seen in Griscelli syndrome type I patients and dilute mutant mice) cause partial albinism (a.k.a. pigment dilution) due to perinuclear melanosome clustering and defects in the transfer of melanosomes from melanocytes to keratinocytes (Hume and Seabra, 2011).

However, in spite of the suggestion that the DPOGS206617 might encode a myosin motor protein, sequence analysis reveals that the similarity between the predicted DPOGS206617 protein and other myosins is rather limited. Briefly, DPOGS206617 encodes a 360 residue protein that appears to contain three IQ motifs (http://prosite.expasy.org/). While the presence of tandem IQ motifs supports the idea that DPOGS206617 could represent a novel pigment transporting myosin, the finding that it lacks an obvious myosin motor domain argues strongly against this. Although IQ motifs are characteristic of the lever arm of myosins they function in Ca2+/calcmodu-
lin signalling and are also found in a number of other types of protein, for example neuronal growth proteins, voltage operated channels, phosphatases and Ras GTPase-activating protein (Bahler and Rhoads, 2002). Thus it is far from clear that DPOGS206617 protein regulates pigmentation in the monarch by an analogous mechanism to that of myosin-Va in mouse. Indeed searching the mon- arch genomic database with mouse myosin-Va protein sequence reveals the existence of another gene DPOGS212512 (http://monarchbase. umassmed.edu/tools3/Get_gene.cgi?id= DPOGS212512) whose predicted product is a 2005 residue protein that shares 47% amino acid identity with murine myosin-Va-related protein, myosin-Vb, and contains all of the type V myosin hallmark domains. It may be of interest in future to investigate the function of this protein in monarch pigmentation even though it is clearly not the gene responsible for albinism in the nivosus mutant.

Nevertheless, this raises interesting questions as to the function of this novel IQ domain containing protein and the mechanism by which it might regulate pigmentation in the monarch butterfly that should be the subject of future research. Furthermore, it will be of interest to know how the muta-
tion(s) underlying the nivosus pheno-
type affect the function of the DPOGS206617 protein as these were not revealed by Zhan et al. in their report.

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