Pterin-based pigmentation in animals

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1. Introduction

Colour is a vital component of the biology of many animals. Through different colourful hues and patterns, animals generate complex phenotypes that mediate their relationship with members of their own species and other elements of the biotic community, as well as their response to specific abiotic features of their ecosystems [1]. Traits associated with the expression of colourful and cryptic displays are vital components of individual fitness, so are thus prime targets for natural and sexual selection. Owing to the relative ease by which colour can be assessed and quantified compared to other traits, the biology of coloration has been extensively studied within the context of animal behaviour, ecology, genetics, developmental biology and evolutionary biology [1]. It also provides easily understandable examples that can improve scientific understanding of evolutionary principles and concepts in biology among the general public.

Colour production can be either pigmentary or structural. Pigmentary colours originate from compounds that exhibit selective absorption of specific wavelengths of light, allowing light of other wavelengths to be reflected. Structural coloration encompasses several phenomena by which colour is generated by the interactions between incident light and an ordered or quasi-ordered nanostructured tissue, leading to constructive or destructive interference for different wavelengths of light. Pigmentary and structural mechanisms often interact to increase display complexity [2,3]. Colour generation by pigments has been extensively studied at multiple levels, and several integumentary pigment classes have been described, the most common of which include melanins, carotenoids, pterins and ommochromes. Despite their biological
importance, these have received unequal attention by biologists. For example, the predominant use of mammalian and bird models, whose pigmentation is largely the result of melanins [4–6] and/or carotenoids [7–9], has hampered our understanding of the evolution of colour to the detriment of other pigmentation types. Pterin pigmentation in particular has been the focus of comparatively fewer studies, and basic gaps persist in our knowledge.

The study of pterins had its genesis in research carried out on butterfly wing coloration. They were first isolated and characterized by Hopkins [10] and Griffiths [13], who ascribed a variety of mostly white and yellow pigments isolated from pierid butterflies (figure 1a,b) to uric acid or its derivatives, and called them ‘lepidotic acid’ (referring to butterflies, Lepidoptera). The interpretation at the time was that these animals were using excretory substances in ornamentation. Their classification as derivatives of uric acid was afterwards disputed by Schöpf & Wieland [14,15], who noted similarities but also important differences in their chemical properties. These authors termed the pigments ‘pterin’, from the Greek πτερον ‘feather, wing’, calling the yellow pigment xanthopterin and the white pigment leucopterin, reflecting their optical properties. The chemical structure of these pigments, composed of a pteridine ring system, was later determined by the work of Purrmann [16,17], Wieland & Decker [16–18]. Knowledge on the diversity of pterins was further expanded by the identification of other similar pigments in subsequent years [19], such as isoaxanthopterin, erythropterin, pterorhodin, drosopterin and isodrosopterin (figure 2a).

Our aim is to provide an overview on pterin pigmentation in animals. Like the better studied melamins and carotenoids, pterins are ubiquitous across animal taxa; unlike melamins, which are more frequently used for cryptic coloration across animals, pterins are more likely to be involved with generating bright pigmentation, serving key advertising roles; unlike carotenoids, they are produced endogenously. Therefore, understanding their biology is key to unravel the processes that promote or constrain the evolution of different coloration types. Important earlier reviews on the chemistry and biology of pterins are available [19,24–28], but these have focused mostly on basic biochemistry or medical aspects. Given the vital importance of colour in animal biology and the ubiquity of pterin pigmentation, we aim to promote reinvigorated interest in this topic in an era when exciting technological developments make the study of pterins as animal pigments a promising avenue to test both long-standing and emerging questions in ethology, ecology and evolutionary biology.

2. Pterin biochemistry

Pterins are heterocyclic compounds (part of the larger pteridine group) in which a pteridine ring system (composed of pyrimidine and pyrazine rings) features an amino group at position 2 and a keto group at position 4. The pterin biosynthesis pathway is composed of three major enzymatic steps that convert guanosine triphosphate (GTP) into tetrahydrobipterin (BH4). BH4, in turn, is an important redox cofactor in the synthesis of tyrosine, neurotransmitters (dopamine and serotonin) and nitric oxide (figure 2b), while also promoting cell proliferation and scavenging of H2O2 [27,29].

Pterins or their derivatives function as cofactors in many enzymatic reactions, and deficiencies in their production is linked with severe health and developmental disorders such as phenylketonuria, neurological diseases and impaired growth in humans and mice. If complete loss of function occurs, premature death or severe phenotypic disorders are common [28].

The first reaction of the pathway converts GTP into 7,8-dihydrodopterin triphosphate (H2NTP), which is then converted to 6-pyruvoyl-tetrahydropterin (PTP), which is finally converted into BH4. Three enzymes (with little sequence identity among them) control these three steps, respectively: GTP-cyclohydrolase I (in humans coded by the gene GCH1), 6-pyruvoyl-tetrahydropterin synthase (coded by PYS) and sepiapterin reductase (coded by SPR). Owing to multiple whole genome duplication events that occurred during the evolution of teleost fish and amphibians, paralogs of GCH1 and SPR have been identified in these groups [30]. In mice a pseudogene of a SPR-like gene has also been identified and characterized [31].

After acting as a cofactor to aromatic amino acid hydroxylases (phenylalanine 4-hydroxylase, tyrosine 3-hydroxylase, tryptophan 5-hydroxylase) and nitric oxide synthase, BH4 is regenerated through the action of pterin-4-alpha-carbinolamine dehydratase 1 (coded by PCBD1, partially redundant with its homologue, PCBD2, [32]) and quinoid dihydropteridine reductase (coded by QDPR). Apart from the ‘de novo’ and ‘regeneration’ BH4 pathways, a ‘salvage’ pathway converts non-enzymatically modified sepiapterin into BH4 through SPR and dihydrofolate reductase (coded by DHFR). Also, the roles of SPR in the ‘de novo’ and ‘salvage’ pathways are complemented by the action of three other enzymes that metabolize the same substrates: carbonyl reductase 1 (CBR1), aldo-keto reductase family 1 member B (AKR1B1) and aldo-keto reductase family 1 member C3 (AKR1C3).

Notably, the major steps in the BH4 synthesis pathway are essentially conserved across vertebrates and invertebrates (having been mostly studied in humans, rodents and fruit flies), and are even strikingly similar to those in many bacteria [33]. The fact that the molecular pathways used for pterin production are nearly identical across taxa suggests that they play vital cellular roles across highly divergent organisms.

3. Pterins as animal pigments

A large variety of pterin compounds are used by animals for coloration [19]. The molecules that are most commonly identified are xanthopterin, isoaxanthopterin, leucopterin, drosopterin and the similar aurodrosopterin, erythropterin and sepiapterin (figure 2a). These metabolites typically absorb light at wavelengths less than 400 nm, but differ markedly in their absorbance at other wavelengths [34]. For example, leucopterin does not absorb light at wavelengths greater than 400 nm, hence the white colour of the wings of many pierids. Detection of specific pterin metabolites in biological tissues is frequently performed through analytical techniques such as high-performance liquid chromatography–mass spectrometry, Raman spectroscopy or absorption spectroscopy, typically comparing the profiles obtained from a tissue sample to standards for each known metabolite. With few
exceptions (such as spheniscin, see below), most coloured pterins are shared by highly divergent animal taxa and impart similar hues, even when present in different tissues. For example, drosopterin underlies red coloration in the eyes of fruit flies and the skin of lizards (figure 1c,h). The colour of these pterins can also be modified in vivo, not only through interactions with other pigments and reflecting structures [35], but also depending on the pH of the cellular environment or the redox state of the molecule [36]. Although in this review we are concerned mostly with the pigmentary function of pterins, they also contribute to animal coloration in other ways, such as scattering light when in crystalline form in vertebrate eyes [37] and as bioluminescent compounds in myriapods [38].

Pterins have been described in many animal taxa (see table 1 for a selected list). Insects are the taxa from which pterins were initially isolated, so multiple instances of pterin-based pigmentation are known [39,40]. In these animals, pterins are usually deposited as granules in the cuticle or the underlying epidermis. In hornets, for example, xanthopterin-containing granules, composed by an outer shell and a core of microfibrils and axoneme, are formed some days before and after the eclosion of the adult form and underlie the typical aposematic yellow colour of these insects [41,42]. In some cases, such as in the silkworm lemon mutant, sepiapterin-containing granules are found in the underlying hypodermis [43]. Pterins are frequently found in butterfly wings, incorporated into the scales. They also have an important role in compound eyes as screening pigments, occurring in ommatidia together with ommochromes to help modulate incoming light towards visual pigments; in parallel, they also impart colour to the eye [44]. In the eyes of Drosophila melanogaster (figure 1c), drosopterins concentrate mostly inside elliptical Golgi-related granules termed pterinosomes, inside which pigment synthesis likely takes place [45,46]. In many insects, pterins accumulate in the eye throughout the adult stage (in many cases linearly), due to minimal decay, which enables their use as biomarkers of age [47]. In other arthropod groups, there are fewer examples of pterin-based pigmentation, though this is likely due to lack of studies. In crustaceans, pterin-based pigmentation has been confirmed in several groups [44,48–50] (figure 1e), while in arachnids they have yet to be isolated ([51], but indirect evidence from microscopy

Figure 1. Diversity of pterin pigmentation across animals. The pigment type for each example is indicated in parenthesis. (a) Gonepteryx rhamni (xanthopterin, yellow); (b) Pieris brassicae (leucopterin, white); (c) Drosophila melanogaster (drosopterin, isodrosopterin and aurodrosopterin, orange-red); (d) Pyrrhocoris apterus (erythropterin and violapterin, orange-red); (e) Armadillidium vulgare (sepiapterin, yellow); (f) Danio rerio (sepiapterin, yellow); (g) Agalychnis dacnicolor (pterorhodin, putatively contributing to green on dorsum); (h) Podarcis muralis (drosopterin, orange-red); (i) Aptenodytes forsteri (spheniscin, yellow). Photo credits are given in the acknowledgements.
and transcriptomics is known). In non-arthropod invertebrates, pterins are also likely to contribute to pigmentation in brittle stars.

Some instances of pterin-based pigmentation in insects are worth singling out. Some butterfly species synthesize pterorhodin, which is uncommon in most animal taxa — apart from butterflies it has been described in frogs, polychaete worms, and likely in the iris of multiple bird species (it is suspected to colour the eyes of the red-eyed vireo, and was detected in the eyes of the common loon (J Hudon 2021, personal communication)). In blue-tailed damselflies, the epidermis harbours a layer with pterin-containing nanospheres, which both absorb and scatter light, contributing to create a range of colours from blue to green and brown. Another special case occurs in males of pierids, in which pterins accumulate in small beads located in ridges and cross-ribs of wing scales. These beads (which vary in size, shape and pterin content between species) allow for increased absorption of short-wavelength light and an increase in the refractive index of long-wavelength light.

Pterins are also associated with pigmentation in almost all of the major vertebrate groups. The disposition of pigmentary cells often seen in vertebrate skin forms the dermal chromatophore unit, which is uncommon in most animal taxa — apart from butterflies it has been described in frogs, polychaete worms, and likely in the iris of multiple bird species (it is suspected to colour the eyes of the red-eyed vireo, and was detected in the eyes of the common loon (J Hudon 2021, personal communication)). In blue-tailed damselflies, the epidermis harbours a layer with pterin-containing nanospheres, which both absorb and scatter light, contributing to create a range of colours from blue to green and brown. Another special case occurs in males of pierids, in which pterins accumulate in small beads located in ridges and cross-ribs of wing scales. These beads (which vary in size, shape and pterin content between species) allow for increased absorption of short-wavelength light and an increase in the refractive index of long-wavelength light.

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Colours can serve multiple functions in animal communication. In intraspecific communication, coloration can signal an individual’s physiological condition, social rank or reproductive state [81]. In interspecific communication, coloration can impart information on toxicity, deflect predators towards non-vital body parts, improve camouflage or promote species recognition [82]. Pterins have been linked to many of these basic functions. Most colourful pterins typically absorb short-wavelength light, reflecting mostly in the yellow-red range (depending however on the scattering properties of the containing medium), which means that they are typically linked to conspicuous coloration. They have thus been mostly associated with functions such as aposematic signalling to predators and as conveyors of individual quality in the context of sexual selection. Of course, conspicuous pigmentation does not necessarily mean signalling is the primary function of pterins: for example, red drosopterins in the eyes of some species of brachyceran flies serve mainly to promote the regeneration of visual pigments [83].

In interspecific communication, pterins have been most frequently linked to aposematic signals, such as those of butterflies. A well-studied example is that of polymorphic wood tiger moth females, whose hindwings range from yellow to red due to the deposition of erythropterins [84]. Experiments show that these females are rejected more frequently by avian predators when compared with non-conspicuous moths used as controls, and this effect is still significant within species, showing that these pigments are functioning as honest signals of toxicity, and evidence is mixed. For example, in tiger moths, there is no association between the extent of erythropterin-containing areas and aposematic coral snakes and many of its Batesian mimics likely arose from convergent evolution of drosopterin production in skin [87,88]. Despite this strong association between pterins and an aposematic function, few studies have explicitly evaluated whether these pigments are functioning as honest signals of toxicity, and evidence is mixed. For example, in paper wasps, brighter yellow coloration is correlated with larger poison glands [89], while in cotton harlequin bugs there is no association between the extent of erythropterin-mediated red colour and toxicity [90]. Another use for bright pterins in predator deterrence is as deflectors: in spiny-footed lizards, the red tails of juveniles are likely to present as eye pigments in ectothermic vertebrates [75] and birds [76,77]. In this latter case, they are deposited in the pigmented epithelium of the iris in close association with reflecting elements such as guanine crystals, or in some cases appearing in crystalline form [37]. Xanthopterin and isoxanthopterin, known to appear in crystalline form [37], xanthopterin and erythropterin in the eyes of some species of brachyceran flies serve mainly to promote the regeneration of visual pigments [83].

| species                        | common name              | clade                        | pterins                              | proposed function          |
|-------------------------------|--------------------------|------------------------------|--------------------------------------|-----------------------------|
| Gonepteryx rhamni              | common brimstone         | Lepidoptera (Pieridae)       | xanthopterin                         | sexual selection            |
| Pieris brassicae               | cabbage butterfly        | Lepidoptera (Pieridae)       | leucopterin                          | sexual selection            |
| Phoebeis argante               | apricot sulfur           | Lepidoptera (Pieridae)       | erythropterin                        | sexual selection            |
| Vespa orientalis               | oriental hornet          | Hymenoptera (Vespidae)       | xanthopterin                         | aposematism                 |
| Drosophila melanogaster        | fruit fly                | Diptera (Drosophilidae)      | drosopterin, isodrosopterin and aurodrosopterin | screening pigment          |
| Pyrrhocoris apterus            | European firebug         | Hemiptera (Pyrrhocoridae)    | erythropterin and violapterin        | aposematism                 |
| Oncopeltus fasciatus           | large milkweed bug       | Hemiptera (Lygaeidae)        | erythropterin                        | aposematism                 |
| Armadillium vulgare            | common pill-bug          | Malacostraca (Armadillidae)  | sepiapterin                          | uncertain                   |
| Platynereis dumerilii          | -                        | Polychaeta (Nereididae)      | pterohodin, nerepterin and platynerupterin | visual pigments            |
| Lucania goodai                 | bluefin killifish        | Actinopterygii (Fundulidae)  | xanthopterin, drosopterin            | sexual selection            |
| Danio rerio                    | zebrasphi                | Actinopterygii (Cyprinidae)  | sepiapterin                          | sexual selection            |
| Agalychnis dacnicolor          | Mexican leaf frog        | Anura (Phyllomedusidae)      | pterohodin                           | camouflage                 |
| Micrurus fulvus                | Eastern coral snake      | Squamata (Elapidae)          | drosopterin                          | aposematism                 |
| Lampropelis elapoides          | scarlet kingsnake        | Squamata (Colubridae)        | drosopterin                          | Batesian mimicry            |
| Acanthodactylus erythrus       | spiny-footed lizard      | Squamata (Lacertidae)        | drosopterin                          | deflection                  |
| Anolis pulchellus              | Puerto Rican bush anole  | Squamata (Dactyloidae)       | drosopterin, isodrosopterin and neodrosopterin | sexual selection          |
| Aptenodytes forsteri           | emperor penguin          | Aves (Spheniscidae)          | spheniscin                           | sexual selection            |
divert attacks from predatory birds away from the body [91,92].

Although pterins are usually associated with conspicuous colours, they can also contribute to camouflage in some species. For example, pterorhodin in phyllomedusine frogs contributes together with other pigments to create the green dorsal hue of these amphibians. Although the exact mechanisms are not well understood, the presence of pterorhodin coupled with reduced melanin in chromatophores leads to increased reflectance of near-infrared light, mimicking the chromatric properties of leaves [93]. Pterins also generate cryptic blue-green-brown coloration in blue-tailed damselflies through a combination of structural and pigmenitary mechanisms [59].

Signalling in a reproductive context has been another of the primary functions ascribed to pterins. Examples of these pigments creating sexually dichromatic signals can be found in insects [35,60,94,95], fish [96,97], reptiles [69,98,99] and amphibians [100]. Sexual dichromatism in a visual trait may not necessarily mean that the trait is implicated in sexual selection; for example, it could be associated with differential susceptibility of males and females to predators leading to enhanced aposematic displays in one of the sexes. However, in most of these species an explanation rooted in sexual selection is the most likely one.

In coloration biology, one aspect that has been the subject of vigorous research is if and how conspicuous visual signals employed in communication function as honest signals of individual quality, social status or toxicity. Much of this attention has been centred on whether coloration acts as a reliable signal of quality because pigments or their precursors are costly to acquire or if it acts as an index due to being inextricably linked to vital physiological processes [101]. Endogenously produced pigments have been frequently shown to have relatively lower signal value, or at least conveying different information about an individual’s status, presumably because their precursors are not as costly to acquire. This debate has been driven in large part by studies in birds [102–104], for which melanin is typically linked to a cryptic function (but many examples show melanins contributing to non-cryptic displays, e.g. [105–107]), while dietary carotenoids are typically used for bright displays. Pterins can play a major role in informing this debate given they are predominantly used for conspicuous signalling, so should be a prime target to test if the relative importance of resource allocation versus linkage to vital pathways is maintained across major pigment types. Production costs of pterins are thought to be negligible, since they are synthesized de novo from the abundant purine GTP; on the other hand, pterin metabolism is vital to multiple physiological functions. Evidence for the association between the intensity or extent of pterin-based coloration and different measures of individual quality has been contradictory [97,108–112]. For example, in pierid butterflies nitrogen intake during the larval phase is correlated with the intensity of leucopterin-based coloration in the adult wing [109]; whereas in male water dragons the intensity of drosopterin-based red colour is negatively associated with parasite resistance and body size [111].

Given this uncertain role of pterins in signalling condition, and since similarly hued carotenoids that more readily correlate with individual quality are present in many species, why are not the latter favoured as a source of ornamentation? A potential explanation is that pterins may compensate for lower environmental availability of carotenoids. In guppies, interpopulation differences in drosopterin concentration serve to maintain a stable, population-specific pterin: carotenoid ratio in a sexually selected signal, thus maintaining the state of the signal across populations [113]. In agamid lizards, environments with lower productivity are correlated with lower carotenoids concentrations, but with higher pterin concentrations, again suggesting that pterins may compensate for lower availability of carotenoids [114]. However, similarly coloured pterins and carotenoids are not particularly correlated in these lizards, which suggest that compensation of carotenoids by pterins may not be a linear process. A clearer understanding of the molecular pathways implicated in generating pterin-based coloration is likely to shed some light on the relationships between colour and what is being signalled (e.g. [115,116]).

For example, knowing the identity of the genes involved in the expression of a conspicuous signal allows testing hypotheses that link the activity of genes involved with the multiple processes underlying signal expression (production, transport and deposition), multiple measures of individual condition and signal content itself to determine if pterin-based colour acts as a signal due to acquisition costs or due to its processing being linked to vital metabolic pathways.

5. Molecular mechanisms underlying pigmentation

The expression of pigment-based colour depends on the development of specialized pigment-producing cells and organelles, as well as on the production, transport and deposition of pigments within and between cellular compartments. Each of these processes depends on the interaction of several genes. A large portion of our current knowledge on the molecular basis of pterin-based pigmentation has been amassed from Drosophila mutants. The first fruit fly mutant described by Thomas Hunt Morgan was white, which featured loss of pterins and ommochromes in the eye [117]. The white locus has since been shown to code for a subunit of an ABC membrane transporter, with mutants having an impaired ability to transfer substrates of pigment synthesis into pterinosomes [118]. Intracellular trafficking of proteins and pterin precursors also mediate other eye colour mutants in this species [119,120], although these tend to impact on various pigment types, not just pterins. Another indirect route to altering pterin pigmentation can arise through impairment of purine synthesis, which impacts the availability of precursor molecules for pigment biosynthesis [121].

Genes specifically linked to pterin biosynthesis have been described from several mutants (figure 2c). One of the most well known is rosy, which maps to xanthine dehydrogenase (XDH), and that is characterized by brown eyes (containing only ommochromes), lacking isoxanthopterin and having reduced drosopterin [122]. XDH has also been shown to oxidize a number of pterins in the wings of pierid butterflies [123], and mutations in this gene are associated with differences in coloration patterns in bumblebees [124]. Isoxanthopterin biosynthesis is also impaired in lex mutants, which lack activity of a yet unidentified dihydropterin oxidase that acts upstream of XDH [22]. Other genes linked to disruptions of key steps in the biosynthesis of drosopterin
and aurodrosopterin in the eye of fruit flies include several homologues of mammalian genes involved with pterin and purine metabolism [125–131] (figure 2c), as well as the fruit fly gene for pyrimidodiazepine synthase [132]. These results suggest that the biosynthesis of colourful pterins shares the initial conversion steps of the main ‘de novo’ BH4 pathway before diverging into parallel pigment-related pathways [23]. In water strider embryos, xanthopterin and erythrop- terin-based pigmentation has been shown to depend on many of the same biosynthetic steps that govern pterin-based eye colour in fruit flies, suggesting a deep conservation of the molecular mechanisms producing these pigments in insects [133].

Important insights into the genetics of pigmentation driven by pterins in insects have also been provided by butterfly models. The silkworm lemon mutant, characterized by an excess deposition of yellow sepiapterin in the epidermis of larvae, has been linked to several mutations in SPR [134]. In the same species, other mutations manifesting altered colour and lethality in second-instar larvae have been mapped to PTS [135,136]. The ‘albi’ polymorphism of female pierid butterflies is caused by variation in the homeo-box transcription factor BarH-1, which interferes with pigment granule formation in wing scales [137]. In the fruit fly, this same gene is also required for pigment granule formation in ommatidia [138].

In vertebrates, most information has been attained through the study of pigmentation in zebrafish, which exhibits alternate blue-yellow coloured stripes, the latter caused by sepiapterin-pigmented xanthophores [139] (figure 1f). A wealth of colour mutants affecting xanthophore development and pigment synthesis have been identified [140], with most studies focusing on the differentiation of pigment cell types from the neural crest and their interactions, uncovering crucial genes for xanthophore differentiation [141–144]. Of particular interest for pigment synthesis, XDH in zebrafish is also likely to act in the oxidation of sepiapterin to iso-xanthopterin and other colourless pterins, which suggests strong conservation in the parallel pathways for pterin pigment production between vertebrates and insects [145].

Recent studies from non-model vertebrates have also yielded key insights. In the common wall lizard (figure 1d), the orange colour morph is controlled by a tissue-specific cis-regulatory allele of SPR associated with increased drosop- terin accumulation in the xanthophores of ventral skin [146]. The exact role of SPR in drosopeterin synthesis in lizards is unclear, since this link has not been established in insect models. In another recent finding, the membrane transporter SLCA11B was shown to regulate pterin-based eye colour in xanthophore-like iris pigment cells of pigeons [147–149]. Interestingly, this gene is also involved in xanthophore differentiation in medaka [150], but the exact cellular and molecular links between these two cases (pigment uptake versus cell differentiation) are unknown. In vertebrates, like in some fruit fly mutants described above, disrupting lysosome-related orga- nelles can also impact pterin-based pigmentation (and other pigment types), as shown in the corn snake [71]. Knowledge on the general molecular pathways that are correlated with pterin pigmentation in vertebrates has also been further com- plemented by gene expression assays in fish [151–153], amphibians [154,155] and reptiles [156].

Pterins participate in vital housekeeping functions (see above, also [27,29]), and impairment of their normal metabolism leading to severe deleterious effects has often been reported in medical studies [28]. Likewise, colour vari- ants related with changes to pterin metabolism are usually associated with multiple pleiotropic effects. For example, in silkworm lemon mutants sepiapterin accumulation is associated with behavioural changes (in locomotor ability) due to impairment of BH4-mediated neurotransmitter production [157]. Fruit fly mutants described above also show frequent pleiotropic effects associated with eye colour change, including lethality [125,126]. Co-option of housekeeping genes is increasingly recognized as a source of pigmentation novelty [158,159], but these developmental opportunities need to be balanced by the need to offset deleterious effects of mutations affecting biosynthesis of BH4 or its essential precursors. In wild populations, tissue-specific regulatory variation is likely to play a major role in diminishing pleiotropic con- strains, as was shown for wall lizards [146] and pierid butterflies [137]. These two examples are classic cases of stable colour polymorphisms associated with alternative life-history strategies and behaviour, so even when non- coding variation affects pterin synthesis in peripheral tissues such as the integument, pleiotropic effects could be expected as a by-product. These and other animal models (both wild and captive) thus yield immense promise to investigate prox- imate and ultimate mechanisms associated with the evolution of pterin pigmentation.

6. Open questions and future directions in pterin research

Many questions remain on the evolutionary and functional implications of pterin-based coloration in animals. For example, there is still limited understanding of the taxonomic extent of this class of pigments, which has been recorded almost exclusively in vertebrates and insects. Given that similar Colourful pterins have evolved in these two highly divergent groups, many other animal lineages could potentially express these pigments. This lack of basic knowledge highlights the challenges, but also the opportunities, that lie ahead in this field.

There is very little understanding on why animals use pterins as signals. While specific functions have been identified in many taxa, it is unclear what underlying properties of pterins make them an often-preferred pigment. Are they just evolutionarily labile, or does signal honesty promote the maintenance of these ornaments once they evolve? They are widespread as aposematic signals, but pterins themselves are not known to be toxic, so is this link strictly maintained through selection? In the context of sexual selection, more work needs to be carried out to understand if, and in what circumstances, colourful pterins signal individual quality. Is nitrogen intake, for example, a limiting factor signalling a trade-off between physiology and orna- mentation (the costly signalling hypothesis), or are colourful pterins used as signals because they are connected with vital functions (the index hypothesis)? In many species, both pterins and dietary carotenoids are simultaneously used for bright yellow-red coloration (the dewlap of anole lizards is one such example), making this a further challenge to understand the context in which either pigment type evolved.
Central questions on the genes and pathways involved with the synthesis of colourful pterins remain. The major steps in these pathways have received a reasonable amount of attention in fruit flies, but generalization to other animals remains elusive. This is particularly true for vertebrates, for which less than a handful of studies have been conducted, despite pterin pigmentation arising convergently multiple times. Major open questions in this regard include whether the parallel pathways that produce these pigments are conserved among animals, or if the central housekeeping genes in the pterin synthesis and regeneration pathways are currently co-opted for pigmentation. Are genes involved with the synthesis of these compounds more readily co-opted for pigmentation, or are mechanisms affecting transport or uptake less likely to lead to harmful pleiotropic effects? Related to this, how do changes in pterin metabolism for pigmentation impact fitness? In many species, polymorphism in pterin coloration is associated with alternative life-history strategies, but a mechanistic explanation for these associations is still lacking. On a more fundamental level, why have colourful pterins never been described in many animal taxa? Does this result simply from a lack of studies, or are some taxa constrained in their capacity to co-opt the pterin pathway for pigmentation?

A crucial factor in answering many of these questions will be the choice of model species. Abundant experimental and analytical resources available for established models like fruit flies or zebrafish can provide additional detailed knowledge, but focusing on alternative, less well-studied taxa that exhibit variation in pterin pigmentation in either natural or domesticated populations could open the door for a more comprehensive understanding of the evolutionary processes implicated in the evolution of these pigments. Particularly promising models discussed in this review include several polymorphic species of butterflies [60,61,84,109,137], odonates [59,160], heteropterans [86,161], fish [152,153] and squamates [99,110,146,156]. Many of these species are amenable to experimentation in the lab, or are relatively easy to access for sampling and studying in the field (or both).

To take full advantage of these opportunities, traditional approaches in ecology, ethology, colour measurement, genomics and biochemistry can be combined with recent technological advances in molecular biology: these include techniques for profiling transcriptomes [162,163], epigenomes [164,165] and metabolomes [166], as well as genome editing [167–169]. For example, to understand if and how a pterin ornament is involved in honest signalling for sexual selection in a given species, traditional measures of individual quality could be integrated with spectrophotometry and cell-level transcriptomics and metabolomics to quantitatively address links between colour variation, physiology and cellular function in tissues involved with pigment production and key fitness traits such as hormone production or gametogenesis. Future research in this field should thus strive for comprehensive, holistic approaches to improve our understanding on the actual signalling content of colour, how it evolves and how it interacts with other aspects of organismal functioning. Generating extensive phenotypic and genomic datasets is becoming increasingly easier and cheaper for non-model species—the time is ripe for advancing pterin research.

Data accessibility. This article has no additional data.

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