**Evolution of Melanosomes and Melanocytes**

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Ronald Okimoto

I thought that it might be interesting to look into the evolution of melanogenesis in order to better understand how the whole thing works, and this section is sort of an ordered compilation of my notes on the subject.

**Melanin:**

Melanins are multifunctional biomacromolecules. This just means that there are a lot of different melanin molecules and polymers of the various molecules classified as melanins, and they do a lot of things besides being useful for display or camouflage. In looking for the genes associated with melanosome production by melanocytes most of the reviews noted some of the varied functions of melanin within the cell, but a comprehensive listing was not attempted by the reviews, likely because they were most interested in pigmentation in vertebrates, but melanin exists in varied forms in the five kingdoms of life on earth. Bacteria, protists, fungi, plants and animals have been determined to make melanin (D’Alba and Shawkey, 2019). I did find what seems to be all the functions of melanin listed and referenced by Mostert et al., 2018, as pigmentation, free radical scavenging, hard radiation protection, a high-adhesive-strength structural component, and may serve as a chelator of potentially harmful transition metal ions. Mostert et al., 2018 also note that melanin can sustain macroscopic protonic and electronic conduction. D’Alba and Shawkey, 2019 noted that neuromelanin was associated with neurons and possibly involved in sensing electromagnetic fields. Ancient single celled organisms may not have had much use for melanin as a pigment until animals with eyes evolved (life likely existed for over 3 billion years on this planet before eyes evolved) but early lifeforms would find the other functions useful.

Bilateral animals may have evolved before around 573 million years ago (estimate from Carlisle et al., 2024 depicted below in Figure 1). We do not know what the embryos of the first bilateral animals were like, but extant taxa are split into two clades deuterostomes and protostomes. They took two different developmental paths to produce tubular lifeforms with a mouth and anus. My guess is that the initial bilateral animal only had one opening that served both functions of ingesting things and expelling waste, and the protostome and deuterostome lineages took two different developmental strategies to further evolve the internal structure of the animal. In protostome embryos the blastopore opening becomes the mouth and the insides develop towards the anus. In deuterostome embryos the blastopore becomes the anus and the insides of the embryo develops towards the mouth. Vertebrates are deuterostomes and Molluscs (cuttlefish) are protostomes. The bilateral common ancestor likely could make melanin, but did not make melanocytes nor melanosomes (D’Alba and Shawkey, 2019).

Melanin likely did not initially evolve for pigmentation purposes, but likely for it’s free radical scavenging and radiation protection abilities. Melanin’s ability to absorb a broad spectrum of light including harmful ultra violet (UV) light would protect the cells, and the broad spectrum of light absorption results in the dark brown to black color of eumelanosomes. Humans are protected from harmful UV light by the tanning response that produces melanin pigment in the skin (Ping et al., 2022). Lifeforms with eyes did not evolve until the time of the Cambrian explosion that started around 538 million years ago. An alternate hypothesis to the sudden diversification of Bilateria during the Cambrian explosion is that it only reflects the evolution of easily fossilizable animals. Carlisle et al., 2024 has their estimates for when the various bilateral animal lineages evolved, and they have multiple lineages existing before the proposed start of the Cambrian explosion including Cordata. Jawless fish may have evolved during the 25 million year period of the “explosion” but jawed vertebrates may have evolved post Cambrian explosion.

Since the reviews that I acquired were mainly interested in vertebrate pigmentation (D’Alba and Shawkey, 2019, Galvan and Solano, 2016, and McNamara et al., 2021) they did not spend much verbiage on the early evolution of melanin biosynthesis among lifeforms and concentrated on vertebrates. Though melanin is made by a diverse array of lifeforms melanin biosynthetic pathways vary between these lifeforms. I found a couple papers that dealt with the evolution of tyrosinase (Aguilera et al., 2013 and Meitil et al., 2025) and the Meitil et al., 2025 paper confirmed what Aguilera et al., 2013 had found. Meitil et al., 2025 called the enzymes polyphenol oxidases, and Aguilera et al., 2013 called them Type-3 or binuclear copper protein family. The copper oxidases likely existed in the common ancestor of all extant life on earth. They are split into three main types (alpha, beta, and gamma) that evolved from a common ancestral enzyme that existed in our bacterial ancestors (Aguilera et al., 2013). All three classes of copper oxidases evolved tyrosinase (TYR) activity. The gamma class (includes vertebrate tyrosinase) split off from the alpha class in one of the common ancestors of Metazoa (Aguilera et al., 2013, Figure 1). The beta class copper oxidase split from the alpha and gamma lineage earlier before Unikonta (includes Amoebozoa, Fungi, Porifera, Protostomia and Deuterostomia) evolved. The Vertebrate tyrosinase (*TYR*) gene evolved from the gamma lineage, while Mollusc (cuttlefish and mussel) *TYR* evolved from the alpha lineage, and Arthropod (insects) *TYR* and hemocyanin evolved from the beta lineage. The story may be complicated by some horizontal gene transfer between lineages. So basically all bilateral animal lineages can make melanin but deuterostomes and protostomes use different TYR enzymes to make melanin.

**Melanosomes and Melanocytes:**

Making melanin in melanosomes may be an ancient biotechnology (Figure 1 has an abbreviated phylogeny relevant to this subject). Cuttlefish produce melanosomes in their ink gland and a class of chromatophores called melanophores. Melanosome production in ink glands has been well studied (Palumbo 2003). What are called melanosomes are membrane bound vesicles derived from the golgi or endoplasmic reticulum of ink gland epidermal cells, and melanin granules form in these vesicles. Vertebrate melanosomes, made in melanocytes, are derived from the endosomal membrane Raposo and Marks, 2007. The cuttlefish melanosomes release the melanin granules into the ink gland lumen by exocytosis, while melanocytes transfer melanosomes intact to keratinocytes. There are melanosomes in the cuttlefish melanin-containing chromatophores (melanophores), and Google claimed that the melanophores are derived from the neural crest as are melanophore and melanocytes in vertebrates, but they are obviously wrong because protostomes do not have a neural crest in their early embryos. Google correctly noted, when asked, that cuttlefish did not have a neural crest. It is likely a mix up because the same name (melanophore) is used for Mollusca and Vertebrata. It is an example of “you can’t believe everything on the internet” and likely applies to some of my opinions. Even with a few similarities it is likely that mollusc and vertebrate melanosomes evolved independently, and their systems depend on different classes of tyrosinase. This makes sense because Mollusca (includes cuttlefish) and Vertebrata evolved their camera lens eyes independently and would not have been able to see the pigmentation differences until after the two lineages had separated. There would have been no reason to evolve color displays and camouflage unless your mate or predators could see it. I have a simplified phylogeny in Figure 1. Cuttlefish use the alpha class and vertebrates use the gamma class of tyrosinase (Aguilera et al., 2013). As noted above the gamma class is a subtype of the alpha class and diverged from alpha before the common ancestor of metazoans existed. Bilateria is only one clade of metazoans. The alpha and gamma class enzymes would have existed in the common ancestor shared by cuttlefish and vertebrates, but the alpha class evolved to be tyrosinase in the cuttlefish lineage, while the gamma class copper oxidase evolved to be used as tyrosinase in the vertebrate lineage.

It looks like melanocyte evolution occurred sometime after chordates had evolved, and that melanosome evolution predates that of the existence of melanocytes. Vopalensky et al., 2012 demonstrated that amphioxus (supposedly has a genome most closely similar to the cordate common ancestor of vertebrates) had melanin pigmented cells associated with their frontal eye, and that these cells were subject to the same pigment inhibitors that disrupted pigmentation in vertebrate melanocytes and retinal pigment epithelium (RPE). They determined that the amphioxus RPE pigment cells have the same embryonic origin as the RPE in vertebrates (neural ectoderm). In vertebrates the RPE cells can produce melanosomes, and RPE cells are derived from the neural ectoderm while melanocytes are derived from the neural crest. Amphioxus does not have melanocytes. Melanosome producing cells derived from the neural crest apparently evolved in an early vertebrate ancestor (Smith, 2020). Lopes et al., 2007 found that RPE cells of mice formed melanosomes that used PMEL17 to form the internal melanosomal protein scaffold during melanosome development. PMEL17 is used to create the melanosome internal protein scaffold into which eumelanin is embedded in some type of stacked array in vertebrate melanocytes. Everything doesn’t seem to be thoroughly worked out at this time, but it looks like melanosomes were involved in evolution of the initial eye spots before the camera lens eye evolved (Vopalensky et al., 2012). As noted RPE cells produce melanosomes, but RPE cells are not considered to be melanocytes and are derived from the neural ectoderm while vertebrate melanocytes develop from the neural crest of the early embryo.

Smith, 2020 notes that when melanosomes were evolving, our cordate ancestors had not yet evolved the neural crest during their embryonic development. These ancestors did develop a neural tube, but they were sessile (bound to a substrate) filter feeders. Evolution of the neural crest is not just associated with pigmentation, but with the evolution from sessile filter feeders into mobile vertebrate predators. The neural crest does not just produce melanocyte stem cells, but is responsible for the production of peripheral neurons, glia (neuronal support cells), and skeletal/connective tissue. Melanocytes evolved during a time when our ancestors were evolving a head and skeleton to support a mobile body and the neural crest likely evolved in our jawless fish ancestors along with melanocytes.

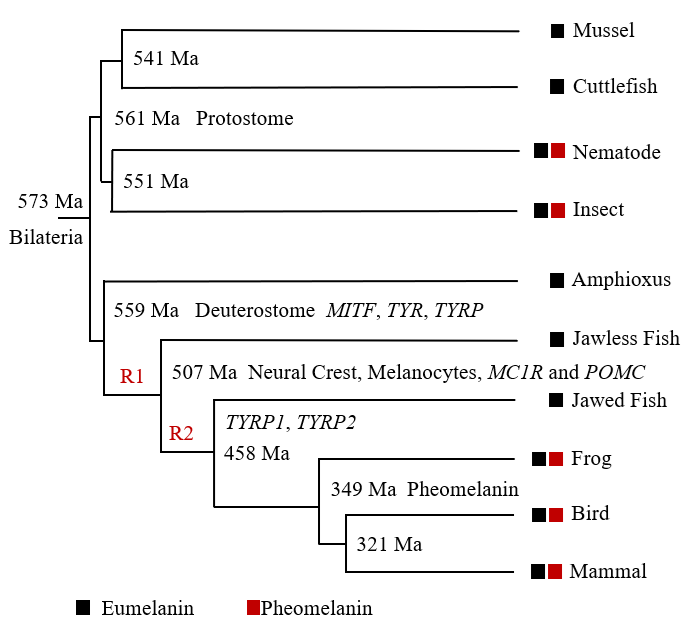


Figure 1. This is a reduced representation of D’Alba and Shawkey, 2019 Figure 1 with some of the information from McNamara et al., 2021 Figure 2. D’Alba and Shawkey, 2019 did not have mussel or nematodes on their figure, but those are the taxa that I could find dated by Carlisle et al., 2024. The divergence estimates are in Ma (million years in the past). I rounded to whole numbers because the precision of the estimates do not seem to warrant any decimal places. I took their mean estimates from their model #1 (Carlisle et al., 2024 supplementary data). They are quite a bit different than the estimates of McNamara et al., 2021 in their Figure 2. I only have Chordata representing deuterostomes, and Carlisle et al., 2024 estimates that deuterostomes evolved around 565 Ma. R1 and R2 indicate the two whole genome duplication events in the vertebrate lineage. The black squares indicate that eumelanin is produced in those lineages. The red squares indicate that pheomelanin is produced in those lineages. The long terminal branches are not to scale and were truncated to fit into a reasonably sized phylogeny. The node branches are set to scale relative to each other.

**Genome duplications:**

First, a digression about homology. Homology is a concept in evolutionary biology that is used to deal with structures shared between species that these different species inherited by descent from a common ancestor. They are inherited by lineage splitting and the same structure is inherited by descent from a common ancestor of the two related lineages. In each speciation event the new species inherits a lot of things from the parent population. For genes there are two types of homologs, orthologs are genes related by descent from a common ancestor, and paralogs are genes that duplicated within the same species. Paralogs are homologous (share a common ancestral gene), but they were not inherited from a direct line of descent from an ancestral species, but instead arose by a gene duplication event. Whole genome duplication creates a lot of potential paralogs. After a genome duplication event there are now 4 copies of the same gene instead of the normal 2 of a diploid organism. Most of the duplicated genes are lost or inactivated in future evolutionary events involving that lineage because they are basically extra genes that can be lost, but some of them evolve to do something a little different and they start their own orthologous gene lineages that are inherited by descent. They are paralogs to the original duplicated gene, but have come to be inherited by descent from a common ancestor during subsequent evolution of the lineage. Tyrosinase (*TYR*) and tyrosinase related protein (*TYRP*) are paralogs due to a gene duplication in chordates (the chordate ancestor of vertebrates had tyrosinase and tyrosinase related protein genes). In jawed vertebrates *TYRP1* and *TYRP2* (tyrosinase related proteins 1 and 2) are paralogs that evolved from *TYRP* that duplicated in the R2 whole genome duplication event described below. The *TYRP1* genes found in extant birds and mammals are orthologs inherited from the same common tetrapod ancestor. Most of the genes in extant organisms are found in gene families whose members are paralogs like *TYR*, *TYRP1*, and *TYRP2*.

The chordate amphioxus genome may best represent the chordate genome that our vertebrate lineage had before two rounds (R1 and R2) of whole genome duplication occurred (references in Braso-Vives et al., 2022). In Figure 1 I have noted where the duplications occurred in the evolution of vertebrates, and some of the information on what melanogenesis genes existed before and after the duplication events. This means that the common ancestor of all extant vertebrates was tetraploid compared to our chordate common ancestor with amphioxus (Carlisle et al., 2024 has this split occurring 559 million years ago. This is before the Cambrian explosion started 538 million years ago) and there was a second duplication (R2) that is shared by all jawed vertebrates making our (including humans) jawed vertebrate common ancestor octoploid compared to amphioxus. Jawed vertebrates may have evolved by 507 million years ago (after the Cambrian explosion had ended around 511 million years ago). These genome duplications are noted in McNamara et al., 2021 Figure 2. Most lineages have lost a lot of those extra genes, but many of those extra genes contributed to the evolution of the diversity that we find among extant vertebrates. There have been subsequent genome duplications that have occurred in some vertebrate lineages, but primates and birds are not among them. Braso-vives et al., 2022 identified over 26,000 protein coding genes in the *Branchiostoma lanceolatum* (amphioxus) genome. They also note that there has been significant small scale gene duplication events in the amphioxus genome similar to the gene duplications observed among vertebrates since the common ancestor with vertebrates existed. There were a lot of local segmental duplications of chromosomes that created all the duplicated genes in *B. lanceolatum* that have occurred since it split off from the lineage that would become vertebrates. Nurk et al., 2022 identified over 19,000 protein coding genes in the telomere-to-telomere human genome sequence (*B. lanceolatum* has more protein coding genes than humans). This means that many of the genes duplicated in the R1 and R2 whole genome duplication events have been lost during the evolution of the vertebrate lineage and a lot of segmental gene duplications have occurred in the *B. lanceolatum* Chordate lineage.

These two genome duplications are important for the evolution of melanocyte pigmentation because the neural crest and genes such as *MC1R* (melanocortin 1 receptor) and *POMC* (proopiomelanocortin) did not evolve until after the R1 genome duplication event and would have evolved from the additional copies of each ancestral gene in the Chordate genome. *POMC* may be a paralog of an ancestral opioid ligand coding gene (Dores and Baron, 2011) and *MC1R* is a member of the family of G protein-coupled receptors with 7 transmembrane regions (Yang et al., 2021. POMC is processed into the melanocortin peptide ligands that bind to MC1R and other melanocortin receptors. Amphioxus can produce melanosomes in their RPE cells as do vertebrates, but they do not have *POMC* nor *MC1R*. They do have genes associated with melanin biosynthesis such as *MITF* (Ji et al., 2024). *POMC* and *MC1R* are found in jawless fish and probably existed before the second full R2 genome duplication. As noted above the neural crest and melanocytes likely evolved in jawless fish. Melanocytes existed before the R2 duplication event that occurred in the common ancestor of all extant jawed vertebrates. McNamara et al., 2021 noted that MC1R was likely initially involved in the regulation of pigmentation in the dorsal and ventral regions of the fish. Fish bellies have less pigment than their backs. This probably served as both camouflage and protection against UV light. From below white bellies are lost in the glare of the light coming down from the surface. Tetrapods also usually produce less melanin on their ventral surface than on their backs.

Tyrosinase (TYR) is required for melanin biosynthesis, but it was doing many other things in amphioxus besides producing melanin in the RPE cells (Pang et al., 2013. In invertebrates TYR has been associated with sclerotization of the cuticle, defensive encapsulation and melanization of foreign organisms, and wound healing. Pang et al, 2013 found TYR expressed in many amphioxus tissues (muscle, epidermis, notochord, ovary, hepatic caecum, pharynx and gill). Characterization of *TYR* gene sequences by Esposito et al., 2012 indicates that the *TYR* gene had already duplicated to create a tyrosinase related protein copy in the chordate lineage before the R1 genome duplication event. This tyrosinase related protein gene was then duplicated during the R1 and R2 duplication events, but *TYR* remained single copy in the vertebrate lineage likely due to loss of the duplicated copies with only one set surviving. McNamara et al., 2021 has the *TYRP1* and *TYRP2* (tyrosinase related protein 1 and 2, respectively) created during the R2 genome duplication event, so one of the duplicated cordate tyrosinase related protein genes was lost and only one of the R1 copies duplicated and survived after the R2 event. This is consistent with the tyrosinase phylogeny of Esposito et al., 2012. The reference cited by McNamara et al., 2021 (Braasch et al., 2009) notes that nearly all the genes related to pigmentation in terrestrial tetrapods are also found in fish. This indicates that melanocytes had evolved to about their current state after the R2 genome duplication event. There was an additional evolutionary step that tetrapods made and that is the production of pheomelanosomes. Fish have eumelanosomes, but not pheomelanosomes. Amphibians, reptiles, birds and mammals all can produce pheomelanin (D’Alba and Shawkey, 2019). Arthropods (insects, shimp etc.) produce pheomelanin, but use different cells and enzymes to make melanin (D’Alba and Shawkey, 2019). Figure 1 should help with tracking when melanogenesis and melanocytes evolved during the evolution of vertebrates.

**Conclusion:**

Protostomes and deuterostomes both produce what are called melanosomes. My opinion is that melanosomes evolved independently in both protostomes and deuterostomes (Figure 1 has the phylogeny). Melanocytes are derived from the neural crest early in embryonic development. The neural crest evolved in jawless fish after the R1 whole genome duplication event. Pigmentation genes such as *POMC* and *MC1R* evolved from among the R1 duplicated genes and jawless fish evolved melanocytes that produced eumelanosomes. After the R2 whole genome duplication eumelanosome producing melanocytes were functioning in jawed vertebrates (all jawed vertebrates were fish at that time in the past) and the fish had nearly the complete modern complement of genes associated with pigmentation. Members of the lobefin fish lineage started to evolve limbs and the lobefin fish lineage that became amphibians was able to evolve pheomelanin biosynthesis and the production of pheomelanosomes in an early ancestor of all extant tetrapods. All classes of terrestrial tetrapods (amphibians, reptiles, birds and mammals) can make pheomelanosomes and can have melanocytes producing the black eumelanin as well as red pigment pheomelanin. *MC1R* had existed since the R1 genome duplication event, but during the transition from water to land MC1R took on an additional new function for controlling the differential production of eumelanin or pheomelainin. The MC1R system was coopted to regulate the production of eumelanosomes or pheomelanosomes in the melanocytes in tetrapods.

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