Review

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Color me bad: microbial pigments as virulence factors

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A hallmark feature of several pathogenic microbes is the distinctive color of their colonies when propagated in the clinical laboratory. Such pigmentation comes in a variety of hues, and has often proven useful in presumptive clinical diagnosis. Recent advances in microbial pigment biochemistry and the genetic basis of pigment production have sometimes revealed a more sinister aspect to these curious materials that change the color of reflected light by selective light absorbance. In many cases, the microbial pigment contributes to disease pathogenesis by interfering with host immune clearance mechanisms or by exhibiting pro-inflammatory or cytotoxic properties. We review several examples of pigments that promote microbial virulence, including the golden staphyloxanthin of *Staphylococcus aureus*, the blue-green pyocyanin of *Pseudomonas* spp., and the dark brown or black melanin pigments of *Cryptococcus neoformans* and *Aspergillus* spp. Targeted pigment neutralisation might represent a viable concept to enhance treatment of certain difficult infectious disease conditions.

Microbes of color

Colors are vital to the sensing of the environment and have evolved in higher living organisms to guide their interactions with others. For example, it is well appreciated that many birds exhibit brightly colored plumage to attract members of the opposite sex, that a chameleon's adaptation to surrounding color is an important means of camouflage, and that the bright coloration of the poison dart frog warn potential predators to stay away. But such explanations cannot be offered to explain why certain microorganisms are pigmented. Because they lack color perception, one must assume evolutionary selective pressures behind the acquisition of pigments that promotes survival independent of their light absorbance, reflection or emission spectral properties (Box 1).

Because colors often provide an easy way of identifying certain microbes, they are often used in names of species. For example, Rosenbach in 1884 named the golden-colored pathogen *Staphylococcus aureus* (Latin, "golden") to distinguish it from nonpigmented staphylococci of the resident skin microflora that he named *Staphylococcus alba* (Latin, "white") [1]. Likewise, the blue-green *Pseudomonas* species not infrequently found in the lungs of patients with cystic fibrosis was given the name *aeruginosa*, which derives from a Latin word denoting the color of copper rust. *Chromobacterium violaceum* not surprisingly elaborates a blue-violet pigment. These hallmark phenotypes not only provide an easy nomenclature for the microorganisms, but continue to be important diagnostic clues in clinical laboratories today for the identification of microbes. Pigments have also played a role in the discovery of infectious pathogens. In the late 1870s, while tending to pathology specimens from patients with malaria in a military hospital in Algeria, Alphonse Laveron, a student of Pasteur, astutely noted that the only common element found in the blood and organs of these patients was a brown-black pigment granule. This major observation was to open the gateway to discovery of the malaria parasite as the infecting agent, a discovery for which Laveran was awarded a Nobel Prize in 1907 (http://www.cdc.gov/Malaria/history/laveran.htm).

With biotechnological advances, contemporary researchers are in a position to study the molecular genetic and biochemical basis for microbial coloration. Investigations using purified pigments or isogenic mutants with altered pigmentation have begun to reveal how these molecules can provide a survival advantage for the pathogen in the host environment and/or produce significant alterations in host cells and immune response pathways (Table 1). In this article, we summarise the current understanding of microbial pigments and their possible role in the pathogenesis of human infectious disease.

Staphyloxanthin of *Staphylococcus aureus*

Among the best-recognised bacterial pigments are the carotenoids that impart the eponymous golden color to the major human pathogen, *S. aureus*. This organism produces multiple carotenoid pigments via a well-described biosynthetic pathway that culminates with golden staphyloxanthin (Figure 1a) as the major product and yellow 4′4′-diaponeurosporene as a minor product [2,3]. Deletion of the gene encoding the early staphyloxanthin biosynthesis enzyme CrtM renders the bacterium colorless and more susceptible to killing by human and mouse neutrophils or whole blood [4,5]. Loss of pigmentation translates to a significant decrease in *S. aureus* virulence in murine skin abscess or systemic infection models [4,6]. Interestingly, 4′4′–diaponeurosporene can be synthesised by several other bacteria upon transfer of just

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Box 1. Some natural functions of microbial pigments

Some natural functions proposed for microbial pigments are given below, with an example reference:

- Protection against ultraviolet radiation [30]
- Protection against oxidants [4]
- Protection against extremes of heat and cold [88]
- Protection against natural antimicrobial compounds produced by other microbes [19]
- Antimicrobial activities against other microbes [37]
- Acquisition of nutrients, such as iron [21]
- Acquisition of energy by photosynthesis (e.g. cyanobacteria) [89]

two *S. aureus* genes, *crtM* and *crtN* [2]. When these genes are introduced into group A *Streptococcus*, the now pigmented tranformants produce large lesions in a mouse-skin infection model, demonstrating that *S. aureus* carotenoids are both necessary and sufficient to promote bacterial pathogenicity [4].

Staphyloxanthin consists of a C30 polyene carbon backbone with alternating single and double bonds typical of carotenoid pigments (Figure 1a); these alternating bonds are able to absorb excess energy from reactive oxygen species (ROS) [7]. Compared with the wild-type parent strain, a nonpigmented *S. aureus* mutant is much more susceptible to killing by hydrogen peroxide, superoxide radical, hydroxyl radical, hypochloride and singlet oxygen [4,5]. Consistent with an antioxidant role, the survival advantage conferred by the *S. aureus* pigment is lost upon infectious challenge of chronic granulomatous disease (CGD) mice or in killing assays using blood of CGD patients with deficient oxidative burst function [4].

Melanin in *Cryptococcus neoformans* and *Aspergillus fumigatus*

Melanin is a pigment commonly found in organisms across many kingdoms (reviewed in Gomez and Nosanchuk [8], Jacobson, [9] and Nosanchuk and Casadevall [10]). Melanins are structurally diverse high molecular pigments made of oxidative polymerisation involving quinones, which can assume three oxidation states. Studies of the paramagnetic properties of melanin identified strong electron-spin resonance signal, which is interpreted as evidence for the presence of stabilised free radicals in biological systems. Thus, melanin can act as a trap for unpaired electrons and has the ability to stabilise potentially harmful unpaired electrons such as those from ROS [11]. A normal component of human skin and hair, melanin is also found to coat the surface of two important fungal pathogens, *Cryptococcus neoformans* and *Aspergillus fumigatus*. Recent mutagenesis studies have confirmed a virulence function of melanin production in these two agents of severe opportunistic infection in immunocompromised patients.

C. neoformans is an encapsulated yeast-like fungus that produces a brown or black melanin pigment by conversion of diphenols or homogentisic acid [12] (Figure 1g); this coloration can be used for rapid identification of colonies on cornmeal agar, a medium commonly used in yeast isolation [13]. *C. neoformans* deficient in melanin production are less invasive and survive poorly in the spleen, liver or brain of infected animals [14,15]. This diminished virulence correlates to a reduced ability of melanin-deficient mutants to resist phagocytic killing *in vitro* [16]. Melanin production impedes phagocytosis of encapsulated *C. neoformans* by macrophages *in vitro* and in a murine lung infection model [16,17]. Melanin also interferes with the action and efficacy of endogenous antimicrobial peptides and pharmacologic antifungal agents against *C. neoformans*. The negatively charged pigment neutralised the activity of neutrophil defensin and other cationic antimicrobial peptides [18], and bound avidly to amphotericin B and caspofungin [19], two front-line drugs used in the treatment of severe fungal infection. Lastly, a ferric iron reduction property of *C. neoformans* melanin, converting Fe^{3+} to Fe^{2+}, could theoretically facilitate ferrous iron uptake through a specific transport system and improve *in vivo* survival [20,21].

Melanin pigment production might also modulate the inflammatory response to cryptococcal infection. When compared with a weakly pigmented strain, infection with

Table 1. Potential virulence functions of microbial pigments

Pigment	Chemistry	Color	Human pathogens	Virulence functions
Staphyloxanthin	Carotenoid	Golden	*Staphylococcus aureus*	Antioxidant, detoxify ROS [4,5]
Pyocyanin	Phenazine-derived zwitterion	Blue–green	*Pseudomonas* spp.	Cytotoxicity [36,37,39] Neutrophil apoptosis [50] Ciliary dysmotility [43] Proinflammatory [49]
Melanin	Polyacetylene or polypyrrine polymers	Dark-brown, black	*Cryptococcus neoformans*, *Aspergillus* spp., *Wangiella dermatitidis*, *Sporothrix schenckii*, *Burkholderia cepacia*	Antioxidant [11,30,31,32] Antiphagocytic [16] Block antimicrobials [18,19]
Porphyrin	Heteromacrocycle	Black	*Porphyromonas gingivalis*	Antioxidant, detoxify ROS [74]
Granadaene	Ornithine rhamno-polyene	Orange–red	*Streptococcus agalactiae*	Antioxidant, detoxify ROS [64]
Violacein	Rearranged pyrrolidone scaffold	Purple	*Chromobacterium violaceum*	Antioxidant, detoxify ROS [69]
Prodigiosin	Linear tripyrrole	Red	*Serratia marcescens*	Immunosuppressant [79]
Hemozoin	β-hematin aggregates	Brown–black	*Plasmodium* spp.	Detoxification [53] Macrophage suppression [56] Pro–inflammatory [58]

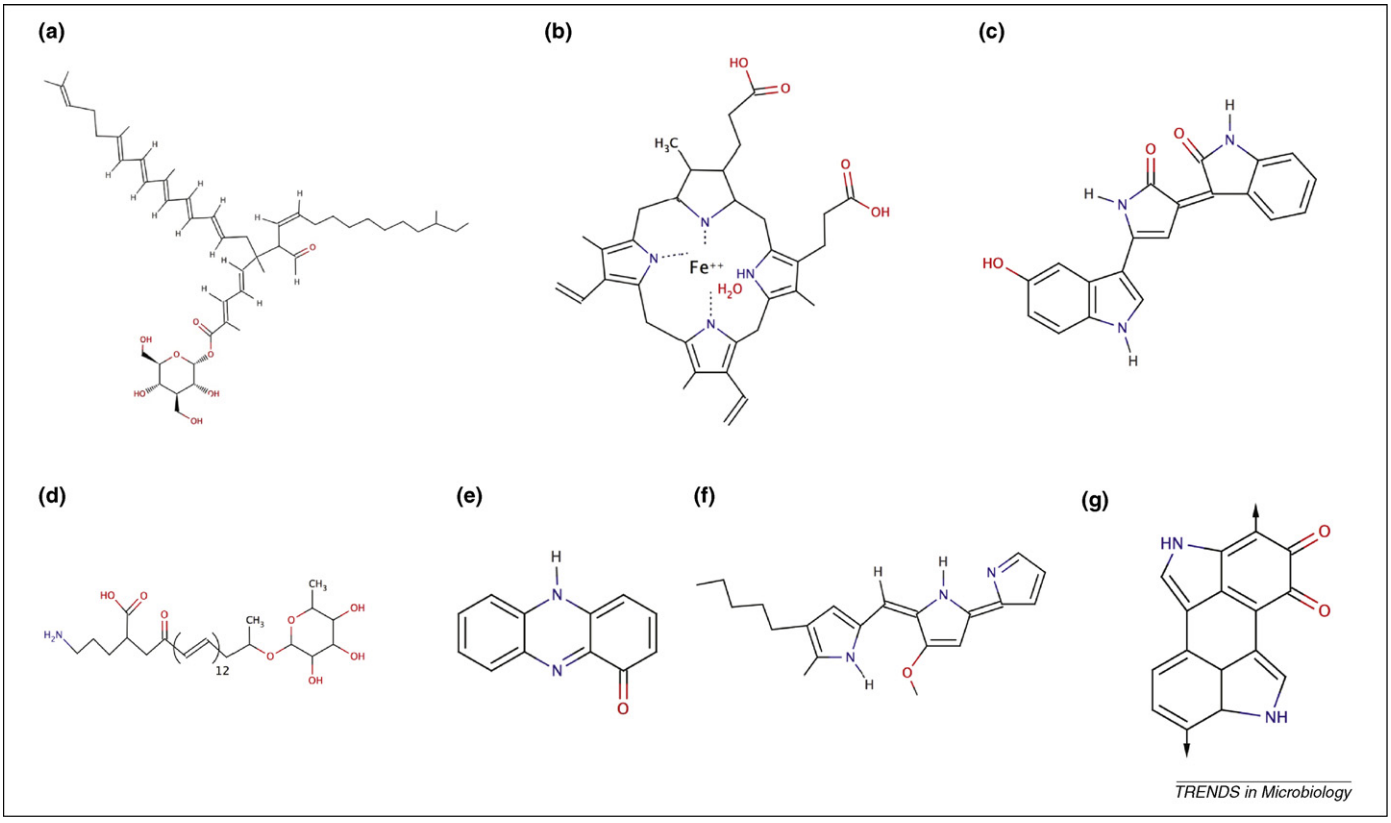

Figure 1. Diverse chemical structures of pigments expressed by microbial pathogens. **(a)** Staphyloxanthin, *Staphylococcus aureus*; **(b)** hematin in malarial hemazoin or the *Porphyromonas gingivalis* pigment; **(c)** violacein, *Chromobacterium violaceum*; **(d)** granadaene, Group B *Streptococcus*; **(e)** pyocyanin, *Pseudomonas aeruginosa*; (f) prodigiosin, *Serratia marcescens*; **(g)** melanin, *Cryptococcus neoformans*.

a heavily melanised strain of *C. neoformans* inhibited the afferent phase of the T-cell immune response as evidenced by diminished tumour necrosis factor (TNF)-α production by alveolar macrophages and decreased expansion of cryptococcus-specific lymphocytes [22]. Further evidence of pigment-mediated inflammatory gene suppression comes from analysis of central nervous system (CNS) injury and cytokine responses following direct intracerebral instillation of an albino *C. neoformans* strain versus a companion melanotic revertant. The pigmented strain produced a lethal infection and massive CNS tissue damage accompanied by minimal cytokine response. Conversely, the melanin-deficient strain never produced a fatal infection, and triggered enhanced CNS levels of mRNA transcripts for interleukin (IL)–12, TNF-α, IL-1β, interferon (IFN)-γ and inducible nitric oxide synthase (iNOS) [23] Mouse immunisation studies using cryptococcal melanin have shown that, despite its amorphic polymeric nature, the fungal pigment can stimulate the immune system to generate specific antibodies [24].

A. fumigatus is a filamentous fungus that elaborates a melanin-like substance during its conidial stage of growth. Survival of conidia within the host is a crucial first step in *Aspergillus* infection. Conidia from an *A. fumigatus* mutant strain lacking pigmentation are more susceptible to killing by oxidants and by human monocytes *in vitro*, and showed reduced virulence in a murine infectious challenge model [25]. Electron microscopic analysis demonstrated that nonpigmented conidia sustained more extensive structural damage within monocytes compared with wild-type pigmented conidia [25]. Targeted mutation of the *A. fumigatus alb1* gene, encoding a polyketide synthase in the dihydroxynaphthalene-melanin pathway, results in an albino phenotype lacking the bluish-green conidial pigment [26]. The nonpigmented mutant was found to be much more susceptible to complement C3 deposition and neutrophil phagocytosis, and was significantly attenuated in a murine intravenous challenge mode [27].

Additional evidence for a contribution of melanin pigments to virulence has been provided in studies of other fungal and bacterial pathogens. Elimination of melanin production by the infrequently encountered dematiaceous fungus *Wangiella dermatitidis* is associated with diminished ability to produce invasive hyphal forms, increased susceptibility to neutrophil killing, and virulence in mouse models of infection [28,29]. Non-melanised conidial mutants of the thermally dimorphic fungal pathogen *Sporothrix schenckii* show increased susceptibility to killing by ROS, reactive nitrogen species or UV light [30]. *Proteus mirabilis*, a Gram-negative bacterial agent of human urinary tract infections, produces a melanin pigment that can act as a free-radical trap [31]. A melanin pigment isolated from an epidemic strain of *Burkholderia cepacia* also possesses antioxidant properties that can attenuate macrophage superoxide production [32].

Pyocyanin of *Pseudomonas aeruginosa*

P. aeruginosa is a leading bacterial pathogen in hospital settings and patients who are immunocompromised as a

result of neutropenia, burns or cystic fibrosis. Many *P. aeruginosa* strains elaborate the blue-green phenazine-derived pigment pyocyanin (Figure 1e), which can impart a greenish hue to the sputum of cystic fibrosis patients with chronic lung infection [33]. In contrast to the antioxidant features of staphyloxanthin and bacterial melanin pigments, *P. aeruginosa* pyocyanin exhibits a paradoxical pro-oxidant property. A zwitterion that can easily penetrate biological membranes, pyocyanin can directly accept electrons from reducing agents such as NADPH and reduced glutathione, then transfer the electrons to oxygen to generate ROS such as hydrogen peroxide and singlet oxygen [34] at the expense of host antioxidant systems such as glutathione and catalase [35]. *P. aeruginosa* mutants lacking pyocyanin are greatly attenuated in both acute and chronic mouse models of lung infection [36], and the remarkable toxic properties of the pigment can be demonstrated to extend to a broad array of target organisms including bacteria, yeast, insects, nematodes and plants [36–39] Inhibition of cellular respiration is clearly one of the important mechanisms of pyocyanin toxicity to bacterial or eukaryotic cells [40,41].

The fundamental ability of pyocyanin to alter the redox cycle and increase oxidative stress appears central to its diverse detrimental effects on host cells. For example, pyocyanin disrupts Ca^{2+} homeostasis in human airway epithelial cells by oxidant-dependent increases in inositol trisphosphate and the abnormal release of Ca^{2+} from intracellular stores. Because Ca^{2+} is important for regulating ion transport, mucus secretion and ciliary beat, these alterations probably have important ramification for *P. aeruginosa* lung infections [42]. The pathway of vacuolar ATPase vesicle transport and protein targeting appears particularly sensitive to pyocyanin action, as revealed in a yeast-mutant library screen [41]. Pyocyanin inhibition of ATPase could directly explain many of its toxicities including ciliary dysmotility [43], disruption of calcium homeostasis [42] and diminished apical membrane localisation of the cystic fibrosis transmembrane conductance regulator (CFTR) [44]. Other potentially toxic effects of pyocyanin include perturbance of cellular respiration, epidermal cell growth inhibition, prostacyclin release from lung endothelial cells and altered balance of protease-antiprotease activity in the cystic fibrosis lung [45].

Many ROS exert a direct effect on NF-kB and other signaling pathways to boost inflammatory cytokine secretion [46,47]. The pro-oxidant effect of pyocyanin can thus augment such innate immune response circuits [48]. For example, pyocyanin increases the release of the neutrophil chemokine IL-8 from lung epithelial cells and upregulates the expression of the neutrophil receptor intracellular adhesion molecule (ICAM)-1 both *in vitro* and *in vivo*; these proinflammatory effects were blocked by treatment with antioxidants [48,49]. In neutrophils, pyocyanin induces a sustained increase in ROS and subsequent decrease in intracellular cAMP, which triggers a time- and concentration-dependent acceleration of apoptosis [50]. As confirmed in studies using wild type and isogenic pyocyanin-deficient mutant *P. aeruginosa*, pigment-dependent acceleration of neutrophil apoptosis and diminished release of neutrophil chemokines might represent an immune suppression mechanism of the pathogen [51].

Hemozoin of the malaria parasite

Malaria parasites, including the human pathogens *Plasmodium falciparum*, *P. vivax*, *P. malariae* and *P. ovale*, accumulate a brown pigment during infection known as hemozoin [52]. In its strictest sense the pigment is not a plasmodial product, but rather the byproduct of heme detoxification [53] (Figure 1b). There exist many theories as to how hemozoin is made, be it by some host processes or specific plasmodial detoxification enzyme [54]. Hemozoin has many functions that could contribute to *Plasmodium* virulence and importantly, several antimalarial drugs including chloroquine work by targeting this heme detoxification/hemozoin synthesis pathway.

The hemozoin pigment appears to exert mixed effects on the host immune system. Ingestion of hemozoin released during schizont rupture by phagocytes has been shown to lead to depression of phagocytosis and oxidative burst, probably as a result of iron intoxication as removal of the labile iron fraction from pigment reduces pigment toxicity [55]. Hemozoin and/or products bound by the pigment also decrease expression of MHC class II antigen, CD54 and CD11c in human monocytes, thereby affecting antigen presentation [56] and blocking differentiation and maturation of human monocyte-derived dendritic cells [57]. Conversely, purified hemozoin activates macrophages to produce pro-inflammatory cytokines, chemokines and nitric oxide [58], which together are thought to contribute to many of the systemic symptoms of malaria. Initial study of this phenomenon linked hemozoin activity to the TLR9 immune activation pathway [59]. Subsequent work has shown that hemozoin itself is inert, as nuclease treatment abolished proinflammatory functions, indicating that the pigment serves as a carrier for plasmodial DNA, which itself is important in activating the host cytokine response [60].

Granadaene of Group B *Streptococcus*

Group B *Streptococcus* (GBS), the leading etiologic cause of severe neonatal bacterial infection, expresses an orange-red pigment that was initially thought to be a carotenoid because its signature triple peak absorbance pattern [61,62]. However a more recent report deduced the pigment structure to be an ornithine rhamnopolyene with 12 conjugated double bonds, dubbed granadaene [63] (Figure 1d). GBS pigment has been shown to enhance GBS survival within macrophages [64], and a study of isogenic pigmented versus nonpigmented GBS showed preferential survival of the pigmented GBS in systemic infection models [64]. Expression of the pigment is invariably linked to expression of another well-known GBS virulence factor, the pore-forming β–hemolysin/cytolysin, through a single genetic locus known as the *cyl* operon [65,66].

Violacein from *Chromobacterium violaceum*

Violacein is a deep violet pigment produced by *Chromobacterium violaceum*, an occasional agent of fatal septicemia in humans [67]. Oxidation and coupling of two

molecules of L-tryptophan by the VioA to VioE enzymes generate the rearranged pyrrolidone-containing scaffold of the final pigment [68] (Figure 1c). Violacein has been demonstrated to possess strong antioxidant properties, and it can protect lipid membranes from peroxidation caused by hydroxyl radicals [69]. Investigation of violacein as a chemotherapeutic agent reveal its capacity to induce apoptosis of leukocyte cell lines [70], and it is conceivable that this property could play a role in immune evasion during severe human infections. Finally, violacein has potent antimicrobial activity against many bacteria and protozoa [71]. Hence, secretion of this pigment might protect against protozoal predation [72] and promote survival of *C. violaceum* in the environment.

Iron porphyrin of *Porphyromonas gingivalis*

The Gram-negative rod-shaped anaerobic bacterium *Porphyromonas gingivalis* is implicated in the pathogenesis of certain forms of periodontal disease. Arginine- and lysine-specific gingipain proteases of *P. gingivalis* degrade hemoglobin to release iron(III) protoporphyrin IX (Figure 1b), which is dimerised to form the micro-oxo bis-haem-containing black pigment of the organism [73]. This pigment can then act as a buffer for *P. gingivalis* against killing by ROS generated by neutrophils [74].

Antimicrobial therapy based on pigment inhibition

Because information is available on the biosynthetic pathways underlying pigment generation in several pathogenic species, the pigments themselves become logical targets for virulence factor-based therapeutic interventions. For example, the first committed step in staphyloxanthin biosynthesis, catalyzed by the CrtM enzyme, involves the head-to-head condensation of two molecules of farnesyl diphosphate to produce the C30 species, presqualene diphosphate [5]. This reaction resembles a key step used in human cholesterol biosynthesis, catalyzed by squalene synthetase (SQS). Solution of the *S. aureus* CrtM crystal structure revealed active site similarities and it was found that several SQS inhibitors developed in the context of cholesterol lowing activity also inhibited staphylococcal pigmentation [6]. One such inhibitor, a phosphonosulfonate, was shown to be effective in rendering *S. aureus* susceptible to ROS and neutrophil killing, and was effective at reducing levels of the pathogen by 98% in a murine systemic infection model [6]. Theoretical advantages of this therapeutic approach would lie in specificity, because the drug would not exert unwanted effects on the normal microflora, and reduced selective pressure for resistance, because the drug only exerts its killing effect in the disease context of an activated host immune response [4,6].

Novel approaches to treatment of cryptococcal infection by inhibition of melanin production have been explored. The systemic herbicide glyphosphate depletes *C. neoformans* melanin levels and prolongs host survival in an experimental mouse model of cryptococcosis [75]. Treatment of *C. neoformans*-infected mice with monoclonal antibodies to melanin reduced the fungal burden 100-fold and improved survival following lethal challenge [76]. Because melanin also binds to amphotericin B and caspofungin, synergistic use of a melanin inhibitor could further improve efficacy of these major antifungal drugs [19].

Microbial pigments as pharmacologic agents

The reddish-pink linear trypyrrole pigment prodigiosin (Figure 1f) is produced by *Serratia marcesens*, an agent of nosocomial infections of the urinary tract and wounds. Prodigiosin has cytotoxic activity against numerous cancer cell lines [77,78] and an immunosuppressive effect on T cells, blocking IL-2 dependent proliferation through inhibition of IL-2-Rα expression [79]. In animal studies, prodigiosin blocks tumor metastasis, delays onset of autoimmune diabetes and arthritis, and improves survival in patients with heart transplant and graft-versus-host disease [78,79]. Violacein extracted from *C. violaceum* is effective against multiple cancer cells including uveal melanoma, colorectal cancer, leukemia and lymphoma cells in culture [70,80,81].

Synthetic melanin and melanin derived from grapes have been shown to downregulate pro-inflammatory cytokine production in the presence of human blood monocytes and in a rat model of adjuvant-induced inflammatory disease respectively. [82,83]. Likewise, a few carotenoids have been shown to activate the steroid receptor RAR and RXR pathways to contribute directly to immune suppression [84]. Whether melanins and carotenoids isolated from microbes have immunosuppressive properties remains to be discovered.

Finally, to engineer natural products most suitable for human consumption, researchers have begun to develop recombinant microorganisms through engineering novel biosynthetic pathways by (i) the combination of compatible genes from different genomes into functional clusters and (ii) the further evolution of new enzyme functions of these genes via experimental mutagenesis, recombination and selection [85,86].

Concluding remarks and future directions

Color in many animals warns of impending danger. From the evidence summarised in this review, it would not be too farfetched to say that pigmentation elaborated by certain microbial species provides a warning of enhanced pathogenic potential. Although phylogenetic diversity of pigmented microbial species and the chemical diversity of the pigments themselves might preclude a single unifying hypothesis for their evolution and persistence, the most common virulence-associated theme identified among microbial pigments is resistance against ROS. The ability of many pigments to stabilise ROS might be inherently linked to the ability of these compounds to confer color sensorium. We postulate that most pigments evolved initially as a mechanism to combat environmental ROS, but over time, these compounds were adapted to serve divergent functions.

Pigmentation might contribute to virulence by allowing a given microbe to evade host immune killing or by provoking inflammatory damage to cells and tissues. The danger of pigmented pathogens might be further heightened in patients with particular immunodeficiencies. For example, patients with CGD harbor mutations in NADPH oxidase resulting in weak phagocyte oxidative burst function; these

Box 2. Unanswered questions and future directions

- Does the structural similarity of certain pigments across kingdoms allow bacteria to modulate host cellular functions or engage in molecular mimicry? Do these properties have important implication for human diseases?
- Many pigments confer resistance to reactive oxygen species (ROS). Because ROS promote inflammation, does the quenching of ROS lead to a reduced inflammatory state? If so, can this action promote microbial colonisation or infection?
- Many of the pigment biosynthetic pathways generate a spectrum of compounds with potentially diverse functions. What are these functions, and can the microbe regulate synthesis of specific product subsets for use under different environmental conditions?
- The fact that some of the biosynthetic pathways involve a great number of catalytic steps and thus metabolic expenditure suggests that pigments are very important. Because such a sophisticated pathway must evolve over time, it is likely that intermediate products of the pathway are important or were once important. How do microbes piece together complex pigment biosynthetic pathways and what are the evolutionary pressures that shape assembly of the final pathway?
- How can a better knowledge of pigment properties and their routes of biosynthesis inform an approach to drug discovery and optimisation, including engineering of novel agents?
- There are many more pigments in the microbial world for which the natural functions or virulence functions remain unexplored.

individuals suffer chronic deep-seated infections with several pigmented microorganisms such as *S. aureus*, *Aspergillus* spp., *S. marcescens* and *B. cepacia* atop the list of etiologic agents [87], perhaps as a result of effective neutralisation of all residual ROS.

Further understanding of the biological properties of microbial pigments will not only enrich our instinctual curiosity about colors, but also provide a scientific basis for therapeutic disarming of the pathogens or for borrowing these multifunctional molecules in pharmacologic applications (Box 2).

Disclosures

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