

Pigments of pathogenic bacteria

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Mini review

Pigments are abundant in nature and can be observed in microbes, animals, and plants. In fact many of the foods that we eat are rich with colorful pigments. As pigments owe their color to conjugated double bonds, these double bonds absorb certain wave lengths of light in the visible spectrum leading to the phenomenon of color, and possibly protection against light exposure and damage of cellular components.¹ These conjugated double bonds have a robust reducing potential that allows them to act as natural antioxidants.¹ Thus they are efficient at neutralizing oxidative stress produced by UV light exposure and also oxidative stress present in the human body or within the environment, and as such have been deemed to be a healthy part of the human diet.^{1,2} Carotenoids are present in fruits and vegetables such as carrots, and as previously mentioned have antioxidant potential. After being taken up by the human body these pigments are transported to various locations and can interact with reactive oxygen species neutralizing this stress. Some pigments prevent DNA mutagenesis protecting genomic material from attack by reactive oxygen species.³ A carotenoid Norbixin found within a seed of a tropical shrub from Brazil has been shown to protect the bacterium *Escherichia coli* from damage due to reactive oxygen species as well as UV light exposure.²

Within the human body the immune system produces a variety of stressors toxic to microbial pathogens that have the effect of inhibiting growth. Some of these stressors include oxidative stress which occurs within phagosomes of macrophages and neutrophils, and pigments present in microbes could protect against the stressors of immune cells. In addition, acidity can occur within phagosomes, as well as within centers of caseating granulomas and at sites of inflammation. There are a number of pigments in various bacterial species which are induced by external stressors such as acidity and pigments provide a survival advantage to the microbes that produce them. Mycobacteria produce pigment in response to exposure to acidic stress, light exposure, and prolonged growth.⁴⁻⁹ A carotenoid from the *Synechococcus species* is produced upon iron restriction stress.¹⁰ Another bacterium *Acinetobacter wofii* induces pigment in response to methanol exposure which may increase oxidative stress.¹¹ In addition hyperosmotic stress as well as acidity induces *Vibrio cholera* to make melanin.^{12,13} This response of increased melanin production may aid survival in aquatic environments and also within the upper gastrointestinal tracts of infected humans where the bacterium is naturally found. Another stressor, antibiotic exposure does not seem to be related to the pigment production as the pigmented phenotype seems to be lost at a higher rate in antibiotic resistant strains of *Serratia marcescens*.¹⁴

In the microbial world pigments can be found in bacteria, fungi, as well as parasites. Within these organisms pigments may additionally serve to stabilize membranes as well as to resist external stressors.¹ Carotenoids seem to partially serve the purpose of membrane stabilization and are present in a variety of bacterial species. Stabilization of the cell wall and protection of lipid compounds of the bacteria may provide an evolutionary advantage by protecting the integrity of the bacterial cell envelope.

Pigments of microbes aid bacteria to resist host induced stress

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which often originates within the host immune system. Immune cells such as macrophages and neutrophils increase the concentration of oxidative species in phagosomes upon engulfment of pathogenic microorganisms to increase oxidative stress which pigments counteract. *Staphylococcus aureus* owes its name to its ability to produce a golden yellow pigment, staphyloxanthin, a carotenoid compound.¹⁵ It produces the pigment constitutively and mutants which lose the ability to produce pigment have a reduced capacity to withstand neutrophil killing.¹⁶ As expected mutants also survive less well in a mouse model of staphylococcal pathogenesis. Staphyloxanthin is hypothesized to help the bacterium resist oxidative stress within the host and to be essential to pathogenesis of the bacterium. In addition pigment production in *S. aureus* is associated positively with the defensive and resistant biofilm growth formation.¹⁷

Mycobacteria have been known for some time to produce a carotenoid pigment. The Runyon system of classification of mycobacteria is based on the division of mycobacterial species' ability to produce pigment, either under UV light exposure, upon extended growth, or not at all, and now acidity.⁴⁻⁹ Many mycobacterial species are environmental and would benefit from pigment production to protect from UV light damage. Pigment may also aid to protect mycobacteria from oxidative damage that occurs during UV light exposure as well as during prolonged growth. Interestingly, we have recently found that acidity also induces pigment formation in mycobacteria.⁹ Many of the mycobacteria that produce an acid induced carotenoid pigment are also environmental mycobacteria and can infect humans. It may be that carotenoid pigments protect mycobacteria from damage due to acidity and/or oxidative stress in the environment and within the host. However, in mycobacteria it has been hypothesized but not tested that carotenoids can indeed protect against oxidative stress.

Therapeutic interventions for pigment producing bacteria could include substances that inhibit pigment production. A cholesterol synthesis inhibitor previously tested in humans was found to inhibit staphyloxanthin production in *Staphylococcus aureus*.¹⁸ This also produced the effect on the bacterium of increasing sensitivity to reactive oxygen intermediates and increased sensitivity to immune cell inactivation.¹⁸ This same strategy may be used with other bacterial cell species that produce pigment in order to increase susceptibility to immune cell killing. This may be important for atypical mycobacterial species that produce human infections such as *Mycobacterium abscessus*, *Mycobacterium fortuitum*, *Mycobacterium*

chelonae, and *Mycobacterium avium* that are typically hard to treat with conventional antibiotics. Compounds which inhibit pigment production may increase the ability to treat these difficult infections, by acting synergistically with antibiotics and increasing their efficacy. However, there is a lack of compounds that have been discovered that inhibit pigment production. This may be an aim of future investigation and research.

Pigments in bacteria seem to be associated with virulence characteristics in a variety of species. This is supported by the fact that inhibiting carotenoid production in *S. aureus* causes this bacterium to be more sensitive to oxidative stress, neutrophil killing, and innate immune inactivation in a mouse model of infection.¹⁸ Pigments are implicated in resistance to immune cell function and aid the bacteria in resisting external stressors such as oxidative stress. Whether pigments aid bacteria in resisting acidity remains to be determined and research into pigment production under different environmental stressors as well as methods designed to inhibit pigment production seems to be merited.

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Conflict of interest

The author declares no conflict of interest.

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