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Functional metabolite assemblies—a review

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Abstract

Metabolites are essential for the normal operation of cells and fulfill various physiological functions. It was recently found that in several metabolic disorders, the associated metabolites could self-assemble to generate amyloid-like structures, similar to canonical protein amyloids that have a role in neurodegenerative disorders. Yet, assemblies with typical amyloid characteristics are also known to have physiological function. In addition, many non-natural proteins and peptides presenting amyloid properties have been used for the fabrication of functional nanomaterials. Similarly, functional metabolite assemblies are also found in nature, demonstrating various physiological roles. A notable example is the structural color formed by guanine crystals or fluorescent crystals in feline eyes responsible for enhanced night vision. Moreover, some metabolites have been used for the in vitro fabrication of functional materials, such as glycine crystals presenting remarkable piezoelectric properties or indigo films used to assemble organic semiconductive electronic devices. Therefore, we believe that the study of metabolite assemblies is not only important in order to understand their role in normal physiology and in pathology, but also paves a new route in exploring the fabrication of organic, bio-compatible materials.

Keywords

Metabolites; Self-assembly; Photonic crystals; Functional amyloids; Supramolecular structures; Nanostructures

Introduction

After an era of genomics and proteomics, metabolites and metabolomics represent the next stage in the exploration of biochemical diversity. Metabolites are intermediates or end products of metabolism comprising a class of small molecules, such as nucleobases, amino

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acids, and vitamins (James 2017). Metabolites participate in key cellular functions and fulfill various roles, including acting as fuel, maintaining cell structure, signaling, defense, and exerting stimulatory and inhibitory effects on enzymes (Harvey and Ferrier 2011; Valle et al. 2016). While often found in their soluble state, the ability of metabolites to self-assemble into distinct entities, giving rise to some of the most complex and diverse structures in nature, is recently emerging as an intriguing phenomenon with applicable implications. Moreover, the inherent ability of metabolites to self-organize goes beyond their physiological function, as it was recently found that metabolite structures may accumulate as a result of several metabolic disorders. These simple building blocks, such as phenylalanine, uric acid, uracil, orotic acid, tyrosine, cysteine, and adenine, can organize by non-covalent interactions, including hydrogen bonding, aromatic interactions, and van der Waals interactions, to form ordered supramolecular assemblies. Remarkably, some of the assembled metabolite structures present amyloid-like biophysical, biochemical, and cytotoxic properties (Adler-Abramovich et al. 2012; Shaham-Niv et al. 2015; Gazit 2016). Canonical amyloids are insoluble fibrillar protein deposits with an underlying cross- β structure initially discovered in the context of human degenerative diseases (Rochet and Lansbury Jr 2000; Makin and Serpell 2005; Chiti and Dobson 2006). Functional amyloids and amyloid-like materials were found to play various roles throughout nature (Pham et al. 2014; Wei et al. 2017), including structural (as in bacterial biofilms and hyphae) or catalytic (as in mammalian melanosomes) functions. Moreover, a wide range of unrelated peptides and proteins have been shown to form artificial amyloid-like fibrillar materials in vitro. These materials are characterized by a well-organized supramolecular structure and have led to the design of many functional nanomaterials (Knowles and Buehler 2011). Similarly, the inherent ability of metabolites to self-associate into ordered structures is now initiating the exploration of their unique properties and functionalities. Here, we describe the assembly of functional metabolites in the biological world and in material science, as well as the physicochemical properties of the assemblies. We further discuss the use and future potential of these assemblies for technological and therapeutic applications.

Naturally accruing functional metabolite assemblies

Supramolecular architectures of metabolite assemblies in biological systems are frequently found in photonic structures. Unlike pigmental colors, structural colors are formed by highly organized multiscale hierarchical architectures. The structural colors observed in biological and other natural materials are often the consequence of interference, diffraction, or selective reflection of light from photonic structures (Adepalli et al. 2017). In these optical systems, the basic metabolite units are maintained by non-covalent interactions constructing highly ordered materials with extraordinary optical properties. Although other purines and their analogues, such as uric acid and isoxanthopterin, are also found as components in natural photonic-based systems, the most commonly used purine in biological structural color systems is guanine (Herring 1994; Gur et al. 2017). As a nitrogenous metabolite, guanine takes part in many cellular metabolic processes and is thus readily available. For example, pigment cells, denoted as iridophores or guanophores, consisting of anhydrous guanine crystal nanoplates, are present in the skin of a wide range of animals of very distinct taxonomic groups. One notable example is the panther chameleon (*Furcifer pardalis*), a

lizard from Madagascar capable of dynamic and reversible color change serving for camouflage, communication, and thermoregulation when excited or relaxed (Teyssier et al. 2015). By changing the osmotic pressure in the cells, the guanine lattice is expanded or reduced, leading to a shift in reflectivity (Fig. 1). The stacked arrangement of the crystalline plates acts as a high-quality reflector that generates structural colors. This efficient color formation is based on the very high refractive index of the guanine crystals, which is 1.83 in the reflecting direction. A similar phenomenon is observed in neon tetra fish, where a variation in the guanine crystal lattice is used to modulate the color. Interestingly, in this system, light is used as the trigger to modulate the lattice spacing of the guanine crystal for color tuning (Gur et al. 2015).

Another interesting example demonstrating the importance of the guanine metabolite-based structures is the image-forming mirror in the eye of the scallop (Palmer et al. 2017b). Scallops possess a visual system comprising up to 200 eyes, each containing a concave mirror, rather than a lens, to focus the light (Fig. 2a). The mirror is composed of a multilayered structure, tiled with a mosaic of square guanine crystals tuned to reflect light penetrating the scallop's habitat. This hierarchical organization is used to control image formation, from the guanine crystals at the nanoscale to the complex three-dimensional morphology at the millimeter level (Fig. 2b–e).

Similar optical metabolite-based architectures are found in the tapeta lucida tissue of some spiders, marine fauna, crocodiles, and other animals with shiny mirror-reflecting eyes. The reflective material varies in chemical composition between different species (Vukusic 2004; Vukusic and Sambles 2003; Ollivier et al. 2004). For example, in animals such as cats and lemurs, riboflavin, the vitamin B₂ metabolite, was found to be the reflecting material, forming rodlet-shaped crystals which are grouped in bundles arranged in a very regular hexagonal lattice pattern (Braekevelt 1990a, b; Coles 1971; Pirie 1959). Riboflavin absorbs light at a low wavelength and fluoresces at 520 nm, which is approximately the maximum absorption of rhodospin (500 nm). Thus, the cat and lemur tapeta lucida appear to not only reflect light but to also divert it into a more useful range by fluorescence. Therefore, the tapetum lucidum provides the light-sensitive retinal cells with a second opportunity for photoreceptor stimulation by acting as a reflecting surface. Any light not absorbed during its first passage through the light-sensitive cells is reflected back again and has a second opportunity to be absorbed, thereby enhancing visual sensitivity at low light levels, which also accounts for the phenomenon of “eye-shine” (Braekevelt 1990b). Another metabolite found to be essential for the function of the tapetum lucidum of other animals, such as dogs and ferret, is zinc-cysteine. In other cases, cholesterol, pteridine, and several lipids were identified as the reflecting materials (Ollivier et al. 2004; Palmer et al. 2017a).

The crystallization of uric acid is often related to high levels of this metabolite in the blood, resulting in its accumulation around the joints, thus underlying the cause of gout disease (Richette and Bardin 2010; Pittman and Bross 1999). Interestingly, ordered layers of uric acid were also found to play a role in reflecting layers of the iridescent cuticle (insect shell) of *Rutelino scarab* beetles (Fig. 3). The reflecting layers have an anticlockwise helicoidal architecture and are responsible for selectively reflecting circularly polarized light with a left-handed (anticlockwise) rotation, thereby causing the metallic-shiny appearance of the

beetles. It was found that circularly polarized light is reflected far more efficiently in beetles incorporating uric acid into their reflecting layers, compared to beetles lacking this metabolite. To facilitate these optical properties of uric acid, an epitaxial incorporation into the helicoidal framework is necessary. When uric acid was removed, a significant reduction in iridescence was observed (Caveney 1971; Finlayson et al. 2017).

The above examples demonstrate how the aggregation of different metabolites is naturally exploited to form complex and sophisticated self-assembling systems. In the next section, we will explore the in vitro manipulations of metabolite assemblies aimed to fabricate functional materials.

Self-assembly of metabolites in material science

Self-assembly of supramolecular metabolite structures provides a means for bottom-up fabrication of various materials. These materials exhibit diverse functional and physiochemical properties which arise from the assembly of the simplest molecular building blocks. The assembly process is dynamic and reversible, resulting in responsiveness and tunable characteristics. Moreover, the use of organic and natural building blocks makes these materials highly suitable for green and bio-compatible applications (Zhang 2003; Lihi Adler-Abramovich and Gazit 2014). For instance, the use of nucleobases and nucleobases-containing molecules as supramolecular motifs is well established (Sivakova and Rowan 2005; Lopez and Liu 2017). Although most of the examples involve the assembly of modified nucleobases or the use of coordination chemistry, there are a few examples that demonstrate the intrinsic ability of nucleobases to self-assemble into entities with unique properties. For instance, the origin of guanine-based hydrogels can be traced back to Bang 1910, when Bang et al. reported that 5'-guanosine monophosphate (5'-GMP) or guanylic acid (a nucleotide used as a monomer in RNA) forms polycrystalline gel aggregates at millimolar concentrations. In 1962, using crystallographic methods, Gellert et al. reported that the gel network contained macrocyclic G-quartet (Hoogsteen-bonded guanine tetramers) building blocks. The unusual ability of this guanine derivative to form planar G-quartet structures via Hoogsteen-type H bonding and their subsequent assembly into columnar aggregates by π - π stacking offer the possibility of generating tunable three-dimensional intertwined fibrillar networks. The ability to tune the properties of these assemblies has led to the finding that 5'-GMP can self-assemble into left-handed columnar aggregates which, at high concentrations, pack into left-handed cholesteric mesophases liquid crystals (Gottarelli et al. 1997; Davis 2004). The same research group also studied the capabilities of folic acid (vitamin B₉) to form liquid crystals (Bonazzi et al. 1993). In this work, it was found that folic acid salts can self-organize in water and generate a supramolecular hexagonal lyotropic liquid crystalline phase with a chiral columnar shape. At a high concentration, the solution becomes birefringent and forms textures similar to those of the hexagonal mesophases formed by guanylic acid phases.

Notably, some metabolites were used for the fabrication of organic-based electronics. For example, Irimia-Vladu et al. (2012) have reported the use of indigo for the fabrication of ambipolar organic semiconductors. Indigo is a dye produced from the *Indigofera tinctoria* and *Isatis tinctoria* plants, which have been cultivated for thousands of years for coloring in

the textile industry. Indigo has very low solubility and a high melting point (390–392 °C) due to stabilization by inter- and intra-molecular hydrogen bonding. These intermolecular interactions of π -domains are responsible for the efficient charge transport that was observed by the authors in highly ordered thin films of indigo, obtained by evaporation. In this work, indigo films were characterized by optical, electrical, and morphological methods, which led to the construction of organic field effect transistors (OFETs) fabricated on natural shellac resin substrates, all made completely from natural and biodegradable compounds (Fig. 4a). The authors calculated a bandgap of 1.7 eV, high and well-balanced electron and hole mobilities of $1 \times 10^{-2} \text{ cm}^2 \text{ V}^{-1} \text{ s}^{-1}$, and good stability against degradation in the air. These inspiring results place the indigo structures in line with the best organic electronic materials (Fig. 4b).

Guerin et al. (2018) have recently demonstrated high piezoelectricity values in certain polymorphs of glycine crystals by efficient packing of the molecules along specific crystallographic planes and directions. Piezoelectricity is the linear relationship between stress and induced electrical charge. Biologically based materials usually present low piezoelectricity values in the range of 0.1–10 pm V⁻¹, which limits their technological applications, compared to 20–800 pm V⁻¹ exhibited by inorganic materials used for piezoelectricity applications, such as lead zirconate titanate, and barium titanate. Guided by quantum mechanical calculations, the authors predicted low permittivity values for γ and β -glycine polymorphs, and assumed it will result in high voltage constants. This predicted quality could make γ and β -glycine suitable for use as sensors and energy-harvesting devices. In order to experimentally test this prediction, an energy-harvesting device was constructed, in which an open-circuit voltage of 0.45 V was obtained after applying a force of approximately 0.172 N to a 324 mm² area electrode (Fig. 5). This is the first demonstration of an energy device composed of undoped amino acids crystals. Furthermore, the authors showed that β -glycine could exhibit substantially higher piezoelectricity coefficient than previously thought (6 pm V⁻¹). A piezoelectric coefficient (d_{16}) of 2×10^2 pm V⁻¹ was experimentally measured, equivalent to standard inorganic piezoelectric materials. These results prove that glycine polymorphs have piezoelectrical properties, which render them suitable for use in energy-harvesting technologies for regenerative medicine.

A summary of the structure and function of the metabolite assemblies reviewed here is presented in Table 1.

To conclude, self-assembly of metabolites presents a new avenue in the construction of biological and bioinspired materials. Although metabolites are often overlooked as building blocks for self-assembly processes, their versatile physical properties, inherent biocompatibility, biodegradability, and low costs make them promising candidates for diverse applications, from the fabrication of optical materials to high-performance electronics. Moreover, basic research of the complex architectures spontaneously generated by various metabolites, both in health and disease, can lead to more profound understanding of their diversified roles, as well as to the development of novel therapeutics for numerous metabolic disorders.

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Fig. 1.

The rearrangement of guanine-based photonic crystals in the panther chameleon serves as the molecular mechanism for controlled color change. Upper panel: Panther chameleon in a relaxed (**a**) and an excited (**b**) state. TEM micrograph of the guanine nanocrystals lattice from panther chameleon iridophores in a relaxed (**c**) and an excited (**d**) state, scale bar 200 nm (adapted from Teyssier et al. 2015)

Fig. 2.

The anatomy and ultrastructure of the multilayer mirror of scallop eyes. **a** An image of five eyes of the scallop. **b–d** Cryo-SEM micrographs of high-pressure-frozen, freeze-fractured cross sections through the eye of *P. maximus*. **b** The mirror viewed perpendicular to the eye axis. White arrow indicates direction of on-axis incident light. **c** The tiled mirror viewed from above. **d** Crystals in adjacent layers, stacked directly on top of each other, viewed in a fracture through the mirror. **e** TEM micrograph of a single, regular square crystal extracted from the eye (adapted from Palmer et al. 2017b with permission)

Fig. 3. Enhanced iridescent of the cuticle. **a–d** The visual appearances of different colored jewel *Chrysina scarab* beetles (adapted from Vargas et al. 2016)

Fig. 4. Indigo field effect transistors. **a** Photograph of ambipolar indigo transistors on shellac. **b** Detailed composition of the OFET composed of completely natural and biodegradable compounds (adapted from Irimia-Vladu et al. 2012 with permission)

Fig. 5.

Piezoelectric properties of glycine crystals polymorphs. **a** Open-circuit voltage response of a layer of γ -glycine seed crystals, orientated along the crystallographic 2-axis. Manual force is applied along the crystallographic 2-axis over time. **b** A layer of γ -glycine seed crystals on a square copper 18 mm $\times$ 18 mm electrode insulated with varnish. **c** Manual compression of a γ -glycine seed crystal layer. Full compression of the layer as shown averaged a force of 0.172 N (adapted from Guerin et al. 2018 with permission)

Table 1
Summary of functional metabolites presented in the review

Name of metabolite	Chemical structure	Function or functional property	Reference
Guanine		Reflecting crystals for structural colors and mirror-like eyes formation	Gur et al. 2015, 2017; Palmer et al. 2017b
Riboflavin (B2)		Reflecting and fluorescent crystals for enhanced night sight	Braekvelt 1990; Coles 1971
Indigo		Thin films acting as OFETs	Irimia-Vladu et al. 2011
Uric acid		Iridescence enhancement	Caveney 1971; Finlayson et al. 2017
Folic Acid (B9)		lyotropic liquid crystals	Bonazzi et al. 1993
Glycine		β and γ -glycerine crystals exhibiting piezoelectricity properties	Guerin et al. 2017
5'-GMP		Hydrogels and cholesteric mesophases liquid crystals	Gottarelli et al. 1997; Davis 2004