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Whence Flavins? Redox-Active Ribonucleotides Link Metabolism and Genome Repair to the RNA World

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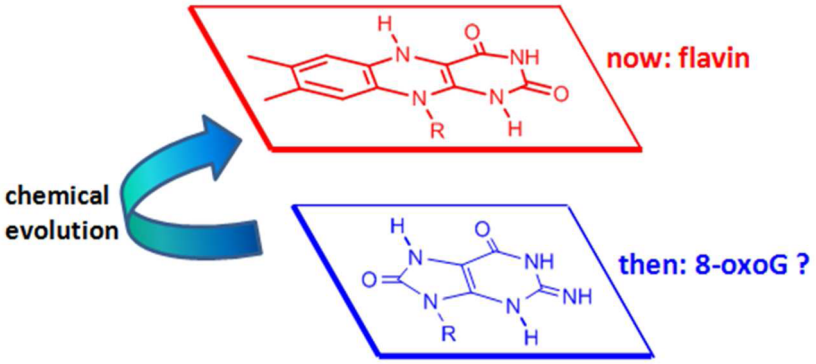

Present-day organisms are under constant environmental stress that damages bases in DNA, leading to mutations. Without DNA repair processes to correct these errors, such damage would be catastrophic. Organisms in all kingdoms have repair processes ranging from direct reversal to base excision and nucleotide excision repair, and the recently characterized giant viruses also include these mechanisms. At what point in the evolution of genomes did active repair mechanisms become critical? In particular, how did early RNA genomes protect themselves from UV photodamage that would have hampered nonenzymatic replication and led to a mutation rate too high to pass on accurate sequence information from one generation to the next?

Photolyase is a widespread and phylogenetically ancient enzyme that utilizes longer wavelength light to cleave thymine dimers in DNA produced via photodamage. The protein serves as a binding scaffold but does not contribute to the catalytic chemistry; the action of the dinucleotide cofactor $FADH_2$ breaks the chemical bonds. This small bit of RNA, hailed as a "fossil of the RNA World," contains the flavin heterocycle, whose redox activity has been harnessed for myriad functions of life from metabolism to DNA repair. In present-day biochemistry, flavin biosynthesis begins with guanosine and proceeds through seven steps catalyzed by protein-based enzymes. This leads to the question of how flavins originally evolved. Did the RNA world include ancestral RNA bases with greater redox activity than G, A, C, and U that were capable of photorepair of uracil dimers? Could those ancestral bases have chemically evolved to the current flavin structure? Or did flavins already exist from prebiotic chemical synthesis? And were they then co-opted as catalysts for repair sometime after metabolism was established?

In this Account, we analyze simple derivatives of guanosine and other bases that show two prerequisites for flavin-like photolyase activity: a significantly lowered one-electron reduction potential and a red-shifted adsorption spectrum that facilitates excited-state electron transfer in a spectral window that does not produce cyclobutane pyrimidine dimers. Curiously, the best candidate for a primordial flavin is a base damage product, 8-oxo-7,8-dihydroguanine (8-oxoGua or "OG"). Other redox-active ribonucleotides include 5-hydroxycytidine and 5-hydroxyuridine, which display some of the characteristics of flavins, but might also behave like NADH.

Introduction

Arguments have been made that modern metabolism reflects the prebiotic chemistry from which life originated.[1,2] Those small molecules that are common to all three kingdoms of life are candidates for having played key roles in early protocells or simple organisms. For example, all life as

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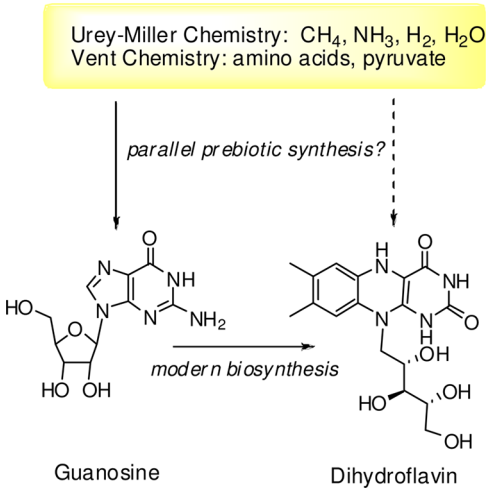

FIGURE 1. The nucleoside analogue riboflavin, shown in its reduced form, might have arisen on prebiotic Earth in parallel to guanosine, or via an evolutionary route from guanosine that mimics its present-day biosynthesis.

we know it uses a relatively small set of α-amino acids, D-sugars, heterocyclic bases, and carboxylic acids of the citric acid cycle. Also among this pool are the flavin-, pterin-, and nicotinamide-containing cofactors which themselves share common features: each serves as a redox-active metabolic coenzyme, and each comprises a heterocycle with an attached ribose-derived fragment. Indeed, two of these cofactors resemble small bits of RNA, except for their 5′-5′ diphosphate linkage, leading H. B. White III to label NAD(P)H and $FADH_2$ as "fossils of the RNA world."[3] The suggestion was that these dinucleotide cofactors evolved at a time when RNA served both genomic and catalytic functions, and were apparently so successful that they were subsequently co-opted during the evolution of protein-based enzymes, remaining as key components of metabolism today. Yarus further hypothesized that the AMP-containing cofactors are the modern descendants of the "Initial Darwinian Ancestor" or IDA,[4] an RNA-like molecule that was capable of replication, evolution, and function.

In vitro selection methods have demonstrated that RNA aptamers can be evolved to bind to flavin and nicotinamide cofactors,[5,6] and ribozymes have been developed that utilize these cofactors in redox reactions.[7,8] These experiments support the hypothesis that catalytic redox chemistry was possible using RNA oligomers and bound heterocyclic cofactors, but they are dependent upon the presence of the heterocycles isoalloxazine (flavin) and nicotinamide. Where did these heterocycles come from? Two possible sources can be postulated: (1) prebiotic synthesis from geochemically plausible reactions of small molecules in a fashion similar to prebiotic routes to purines and pyrimidines,[9−12] or (2) evolution of already existing purines and pyrimidines into more redox-active derivatives that became the present-day cofactors. The first scenario suggests coevolution of cofactors and nucleotides; the second suggests that RNA bases came first (Figure 1). Although an abiotic route to flavin-like compounds has been reported by heating mixtures of amino acids to 150−300 °C,[13−15] flavins do not so far appear in analyses of carbonaceous meteorites where purines have been found[16,17] or in deep-sea hydrothermal vents, although their abiogenesis has been discussed.[18−20] In contrast, the evolutionary route to flavins as descendents of purines parallels the current biosynthetic pathway in which flavin mononucleotide (FMN) and pterins (biopterin, folate, etc.) are derived from GTP (Figure 1). Martin points to a conundrum with pterin biosynthesis from guanosine; the biosynthesis of guanosine requires the pterin-derived cofactor folate for its own biosynthesis![18] A potential alternative to this paradox is that other RNA bases, besides A, C, G and U, played roles in redox catalysis prior to the chemical or biological evolution of flavins, pterins and nicotinamide.

In this Account, we consider alternative RNA bases with flavin-like activity that may have been present as simple derivatives of known RNA bases, or alternatively, could have been generated independently as part of the prebiotic library of RNA bases. Allowing nucleosides containing these bases to enter the network of RNA oligomers might have conferred advantageous photochemical and redox properties to RNA that would have been an evolutionary driver for generation of more ideal redox cofactors.

8-Oxopurines Parallel Flavins

Two key features of flavins that govern their biochemistry are the ability to absorb blue light (300−400 nm) and a relatively low redox potential for the reduced form, dihydroflavin (−0.1 V vs NHE). The guanine heterocycle is a reasonable starting point for evolution of a flavin mimic because it has the lowest redox potential among the known RNA bases (1.3 V vs NHE).[21] Both the redox activity of G and its UV absorbance spectrum are modulated by secondary structure in an oligomer: stacking of G against a 3′ G in a B-form duplex lowers its redox potential, making GG sequences more susceptible to oxidation,[22] while arrangement of G-rich sequences into stacked quadruplexes red-shifts the UV absorbance from 260 to 295 nm. Indeed, a G quadruplex in an evolved DNAzyme was found to mimic the repair activity of the flavin in photolyase.[23,24]

Simple chemical transformations of guanine that augment these properties include hydrolytic and oxidative

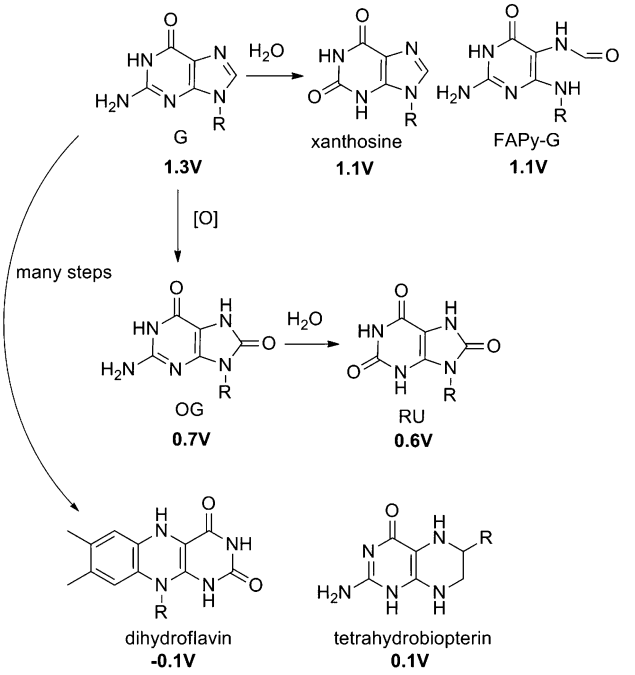

FIGURE 2. Chemical transformations of guanosine that yield redox-active ribonucleotides. R = ribose derivative.

reactions, as shown in Figure 2. Hydrolytic deamination of G yields xanthosine with a corresponding 200 mV reduction in potential. Ionizing radiation or Fenton chemistry invokes hydroxyl radical addition to C8 of G that, under overall reducing conditions, leads to the ring-opened product FAPy-G, which has a similar redox potential to xanthosine. In contrast, the same addition of hydroxyl radical followed by a second one-electron oxidation yields 8-oxo-7,8-dihydroguanine (OG). This single step has a dramatic impact on redox potential, a lowering of about 600 mV at pH 7, and somewhat more at pH 9.[25] One further step, the hydrolytic deamination of the N^2 amino group to give ribofuranosyl uric acid (RU), would also provide a modest enhancement in redox activity over OG.

Closer inspection of OG and RU also suggested that these nucleosides could exhibit flavin-like activity. The UV spectra of both are red-shifted compared to G, exhibiting a longer wavelength band that extends above 300 nm (Figure 3). Dihydroflavin absorbs broadly in the region of 300−450 nm (λ_{max} = 300, 350 nm).[15] While UV light below 300 nm is damaging to RNA causing principally pyrimidine dimers, the longer wavelength absorbance of OG, RU, and flavins could permit photoredox chemistry without concomitant RNA damage.

Additionally, we noted parallels in the structure and chemical reactions of 8-oxopurines and flavins (Figure 4). Perhydroxylation of OG by singlet oxygen or superoxide

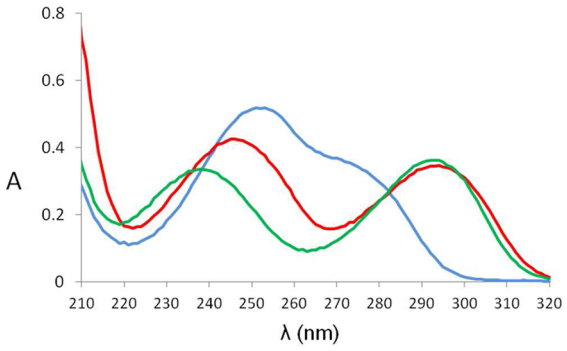

FIGURE 3. UV absorption spectra of ribonucleosides G (blue), OG (red), and RU (green) at 0.03 mM concentration in aqueous buffer, pH 7.

proceeds at C5 to the presumed reactive intermediate OG^{OOH} that is further decomposed in water.[26−28] Similar reactions occur with dihydroflavin leading to perhydroxylation at C4a,[29] the equivalent position in the flavin to C5 of the purine (Figure 4A). Two-electron oxidation of OG leads to the intermediate OG^{ox} that rapidly adds water at C5 and rearranges to a spiroiminodihydantoin structure Sp; this pathway is accelerated at higher pH.[30] Unlike OG^{ox}, the two-electron oxidation product of dihydroflavin is stable to hydrolysis, although at higher pH, a similar rearrangement to a spirohydantoin has also been described (Figure 4B).[30]

Given the strong parallels between flavins and 8-oxopurines in exhibiting similar physical and chemical properties, it seemed plausible that 8-oxopurines might also participate in metabolically relevant pathways as flavin mimics. In such reactions, OG would mimic the reduced form of the flavin, as in $FADH_2$. The corresponding oxidized form of OG, OG^{ox}, is not stable and adds water very quickly to yield hydantoin products. Similarly, RU^{ox} also undergoes decomposition to irreversible products.[31] Therefore, we sought reactions in which OG or RU might mimic the reductive capability of $FADH_2$ rather than the oxidative ability of FAD. The catalytic role of $FADH_2$ in reductive repair of cyclobutane pyrimidine dimers (CPDs) in DNA was an attractive target after which to model such a reaction.

Genomic Damage and Repair on Early Earth

The literature suggests little about active repair of the RNA world genome,[32] although it is certainly critical for the extant DNA genome. Unless RNA replication and catalysis were very fast, either repair or protection against damage must have been important because the chemical instability of the bases would have made error catastrophe profound.[33] Perhaps, then, there was an early driving force for repairing such base damages as might have been prevalent on early Earth.

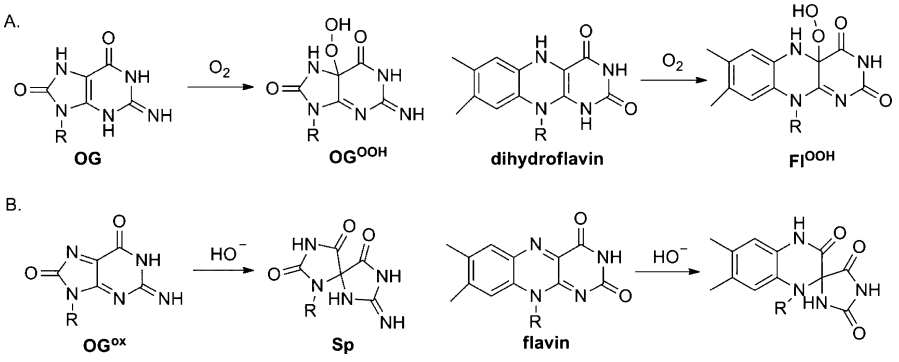

FIGURE 4. (A) Hydroperoxide formation from dioxygenation of OG or dihydroflavin. (B) Spirocyclic rearrangements of oxidized OG and flavins facilitated by basic conditions.

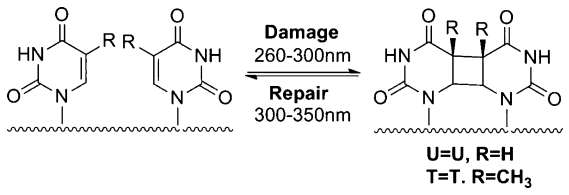

FIGURE 5. Formation and repair of CPDs.

In alkaline hydrothermal vent conditions, metal-catalyzed reductions could have taken place, destroying the aromaticity of nucleobases. On the surface of the planet, protection from UV light must have been extremely important. Three general types of nucleobase chemistry emerge from UV photochemistry: (1) Hydration of pyrimidines, a reversible reaction, except that hydration of C mediates its deamination to U; (2) CPD formation (Figure 5; CPDs are designated "N=N" to indicate the two new bonds formed between adjacent NN bases), along with the related 6–4 photodimers, and (3) oxidative damage. Although the atmosphere of early Earth did not contain the present-day levels of O_2, intense UV irradiation of ice leads to formation of H_2O_2,[34] which in the presence of reduced Fe or Cu provides Fenton reactions, that is, hydroxyl radical generation. Thus, one might speculate that both hydroxylation of bases (G to OG, A to OA, C to 5-OH-C, U to 5-OH-U) and photodimers (U=U, C=U, 6–4 dimers, etc.) could have been common.

Protection of nucleobases from photodamage can originate in several ways. First, having extremely short excited state lifetimes is advantageous because it helps suppress chemical degradation pathways that might arise from the excited state.[35] Studies have shown that G, A, and other purines including xanthine do indeed have short excited state lifetimes that are generally less than a few picoseconds.[36] Second, evolution of a photorepair mechanism for reversing the photocyclization to pyrimidine dimers would restore the original pyrimidines present in an RNA strand, facilitating correct replication and translation of the strand. Photolyase, an $FADH_2$-containing enzyme of very ancient origin, does exactly that.[37] Model studies with flavins covalently attached to CPDs or oligomers containing CPDs indicate that the protein is merely a scaffold; the same catalytic chemistry can be carried out by the reduced flavin cofactor in the presence of light.[38,39] Our goal was to examine whether 8-oxopurines, by virtue of their redox activity and red-shifted absorption spectrum, could substitute for the flavin in a photolyase-like repair system, even without the need for a protein to assemble the substrate and catalyst.

8-Oxoguanosine Mimics $FADH_2$ in Photolyase Activity

Because of the ease of incorporation of both 8-oxo-7,8-dihydro-2′-deoxyguanosine and the *cis, syn*-thymine dimer into any oligodeoxynucleotide sequence context via solid-phase phosphoramidite chemistry, we elected to study first the photorepair of CPDs in DNA duplexes. Lacking ready access to the corresponding U=U phosphoramidite, we conducted studies with only selected RNA sequences by in situ photochemical preparation of U=U in intact RNA strands, which necessitated placement of OG in the opposite strand. In the DNA studies, irradiation of T=T-containing duplexes using a UV light source centered at 313 nm and with wavelengths below 300 nm cut off by a filter led to repair of the T=T lesion, regenerating undamaged TT, in a process that displayed first-order kinetics.[40] For the most reactive duplexes, the T=T dimer was about 50% repaired in 25 min, with a corresponding quantum yield of ~1%.

The rate of repair was highly dependent on the location of OG and on its base-pairing partner (Figure 6.) When T=T was placed in the same strand as OG, it was 3–4× more rapidly repaired compared to having OG in the complementary strand (Figure 6, **4A** vs **1A** and **3** vs **2**). OG stacked on the

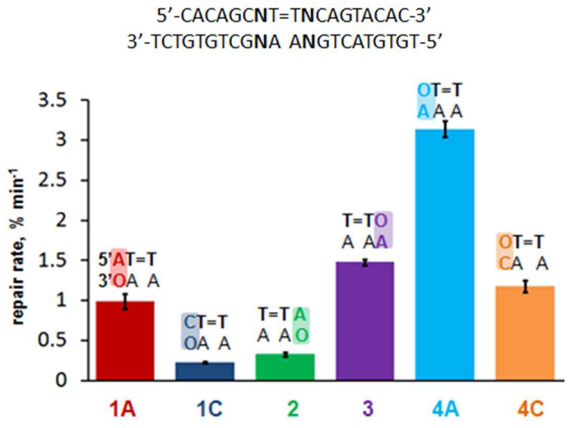

FIGURE 6. Rates of photorepair of *cis,syn*-thymine dimers (T=T) with OG:C or OG:A base pairs (N:N) on the 5′ or 3′ side of the CPD.[40]

5′ side of T=T was ~3× more efficient at photorepair than when located on the 3′ side (Figure 6, **4A** vs **3**), and inspection of a crystal structure of B-form DNA containing a T=T lesion indicates that there is a greater disruption to base stacking on the 3′ side.[41] Other studies have shown that formation of an exciplex between T and a neighboring purine (G or A) can inhibit formation of T=T.[42,43] The importance of base stacking between OG and the CPD is underscored by the difference in reaction rates between T=T repair in DNA vs U=U repair in RNA in the same sequence context. For example, photorepair of U=U in the **1A** sequence context was 2× slower in an RNA:DNA hybrid duplex and another 4× slower in an RNA:RNA duplex, both of which are likely A-form helices that present base stacking between adjacent bases of the same strand.[40]

Interestingly, OG base paired with A was 2−3× more effective at repair than OG paired in a Watson−Crick fashion with C (Figure 6, **1A** vs **1C** and **4A** vs **4C**). We speculate that the base-pair effect is due to the rapid decay of the excited state of OG via proton-coupled electron transfer within the OG:C base pair. Such an effect has been described for G:C base pairs in which the N1 proton on G is transiently transferred to N3 of C.[44] If the same mechanism operates in an OG:C base pair, the excited state lifetime would be shortened accordingly (Figure 7) For an OG_{syn}:A_{anti} pair, the PCET deactivation mechanism might be less efficient because the N7 proton of OG is less acidic, at least in the ground state, and the N1 of A is less basic than the corresponding partners of the OG:C base pair. Importantly, the electron affinity of A is less than that of pyrimidines, so electron transfer within the OG:A base pair is less favorable. These factors together explain the higher efficiency of OG:A for photoinduced electron transfer to a nearby T=T or U=U.

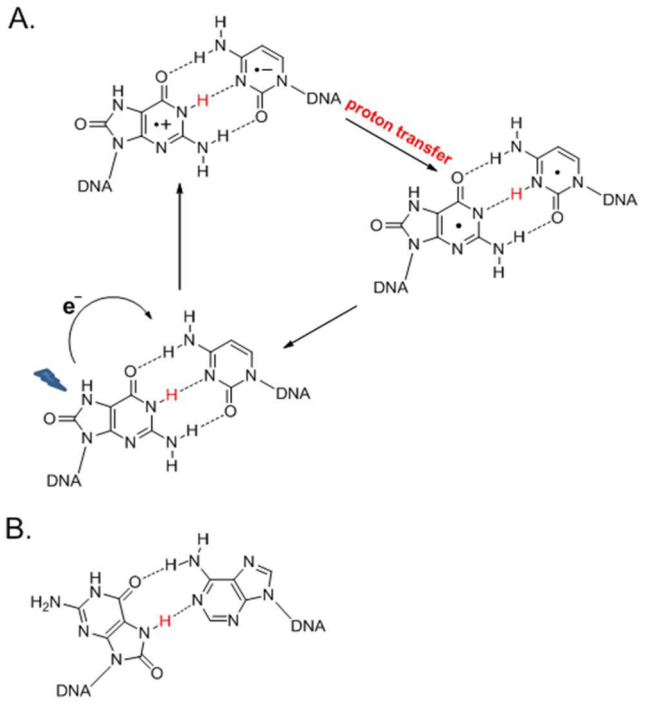

FIGURE 7. (A) Proton-coupled electron transfer is proposed to shorten the excited state lifetime of the OG_{anti}:C_{anti} base pair. The key hydrogen is highlighted in red. (B) PCET in OG_{syn}:A_{anti} would require transfer of a less acidic H (red) to a less basic N.

Overall, these observations provide insight into the mechanism of OG-mediated photorepair of CPDs.

Mechanism of CPD Repair

Photolyase is one of the most extensively studied enzymes by crystallographic, computational, and photophysical methods.[37,45] In the well documented mechanism, the excited state of the enzyme-bound cofactor, $FADH^-$, transfers an electron to the bound T=T substrate, creating $FADH^\bullet$ and the radical anion $[T=T]^{\bullet-}$, which rapidly undergoes asynchronous cleavage of the two cyclobutane σ bonds, forming a ground state T adjacent a $T^{\bullet-}$. Subsequent back electron transfer regenerates $FADH^-$ and the repaired TT-containing strand. If a similar mechanism is operating for OG colocated in a T=T-containing duplex, the mechanism could be summarized as shown in Figure 8.

Support for the mechanism outlined in Figure 8 was obtained in several key experiments.[40] First, the repair of CPDs by OG is catalytic in OG. Using sequence context **1A** (Figure 6) in which OG is placed in the complement strand near the T=T lesion, we observed turnover catalysis of the OG strand in the presence of excess T=T strand by using multiple cycles of light (repair)−heat (denature)−cool (reanneal). It was verified that the presence of OG was

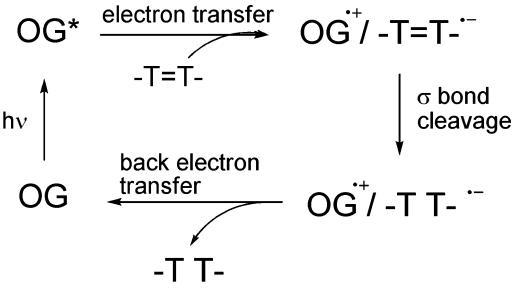

FIGURE 8. Proposed mechanism for photoinduced repair of CPDs by OG by analogy to photolyase.

required for repair; no reaction was observed for duplexes containing G instead of OG. Additionally, the integrity of OG was examined by HPLC after approximately 50% repair had taken place, and none of the characteristic decomposition of OG to produce hydantoin products was observed.

Second, we examined the distance dependence and directionality of the proposed excess electron transfer process. It has been well characterized in other laboratories that while electron hole transfer is more efficient in the 5′ to 3′ direction, excess electron transfer prefers the 3′ to 5′ direction.[46−48] At first glance, the preference for placement of OG on the immediate 5′ side of T=T compared to the 3′ side appears to negate the mechanistic hypothesis. However, studies with OG not directly adjacent the lesion displayed a steeper distance dependence on the 5′ side compared to the 3′ side. Combined, these results support the electron transfer mechanism in two modes: (1) when OG is directly adjacent T=T, a longer-lived exciplex is formed with OG well stacked on the 5′ side, and (2) when OG is more distant, repair is more efficient when it is located 3′ to the T=T lesion. Overall, the features of OG appear to recapitulate the trends of a flavin in repairing CPDs in basic characteristics, if not in magnitude. Yet, additional modifications of the purine structure appear to be required to optimize the efficiency of photoinitiated electron transfer.

Photoredox Activity of Urate and Oxidized Pyrimidines

Can we take 8-oxoguanosine a step further toward a better flavin mimic? Hydrolytic deamination of the exocyclic amine of OG leads to ribofuranosyl uric acid (RU, Figure 2) with a slightly lower redox potential and a higher acidity such that the purine is deprotonated forming urate ($pK_a \sim 6$), akin to $FADH^-$, the active form of the cofactor in photolyase. We anticipated that RU would be a more active catalyst for photorepair of CPDs; however, this purine has so far resisted our attempts to convert it to an appropriately protected phosphoramidite for incorporation into synthetic oligonucleotides. Nevertheless, we were able to perform a nucleoside study to compare the ability of OG versus RU nucleosides to repair photochemically the T=T or U=U lesion.[49] Surprisingly, RU was no better than OG in the pH range where it is anionic and OG is not (pH 5−8), and as the pH of the reaction was increased to approach the pK_a of OG (8.6), the reaction rate for OG accelerated dramatically, but that of RU remained constant. Both RU and OG remain unchanged after prolonged irradiation as indicated by HPLC, and therefore, the low reactivity of RU is not due to a competing pathway of decomposition. Thus, a preliminary conclusion is that deamination of the N^2 amino group, which occurs along the biosynthetic pathway of GTP to isoalloxazine, does not increase the photolyase-like activity of OG.

Xanthine was also considered as a potential flavin mimic; however, it does not display the longer wavelength absorption band in the UV spectrum that is characteristic of OG and RU. Nevertheless, the redox chemistry of xanthine presents an interesting entry into metabolism. The enzyme xanthine oxidase involves FAD, a molybdenum complex, as well as iron−sulfur clusters, acting as a mini-electron transport system as it converts hypoxanthine to urate. The high abundance of hypoxanthine further suggests that 8-oxo derivatives of this heterocycle should also be investigated. Although the addition of an oxo group at C2 of hypoxanthine (yielding xanthine) does not lead to the generation of a long wavelength absorption band, the introduction of an oxo group at C8 likely would. The redox chemistry of this heterocycle has not been studied.

The idea that oxidized pyrimidines might behave in some fashion as redox cofactors was first described by Yanagawa and co-workers.[50] The radiation damage product 5-hydroxycytidine (5-OH-C) was found to be a catalyst for oxidation of NADH using ferricyanide (Fe^{III}) as the terminal oxidant. Both 5-OH-C and its uracil analogue 5-OH-U have redox potentials in the same range as OG and RU,[51] and additionally they show UV absorption bands shifted above 300 nm. As such, they are additional candidates for photochemical oxidoreductase activity, although their structures deviate quite far from the biosynthetic pathway to flavins or nicotinamide.

Grand Challenges and Future Prospects

A challenging aspect to the proposal of 8-oxopurines as precursors to flavins is that neither OG nor RU is found on the biosynthetic pathway from GTP to riboflavin. Despite the fact that one simple transformation, G to OG, confers flavin-like properties to the nucleoside, this pathway overall is a

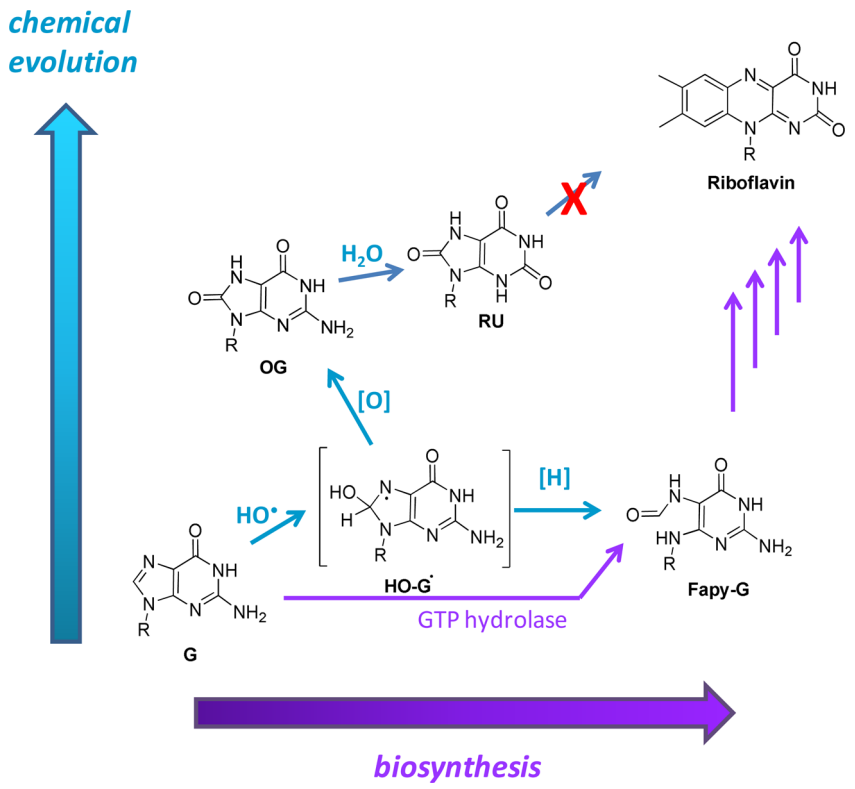

FIGURE 9. Biosynthesis can provide clues to the chemical origin of riboflavin as a redox ribonucleotide cofactor; however, the two processes need not be exactly parallel. Here we note that biosynthesis chose the ring-opening Fapy-G route toward flavin, even though this initial intermediate is less evolved toward redox activity than the related hydroxylation product OG.

dead end (Figure 9). There is no good way to hydrolytically open the 5-membered ring of the purine when it already has been oxidized to a urea. Ureas are notoriously stable toward hydrolysis; witness the fact that urease as an enzyme is deemed catalytically potent (10^{14} rate acceleration), largely because the background reaction is so incredibly slow. A better route, and that selected as the biosynthetic route to riboflavin, would be to open the imidazole ring of G first. Accordingly, the first intermediate on the biosynthetic pathway to riboflavin is Fapy-G,[52] a heterocycle that, coincidentally, is also formed by hydroxyl radical attack at C8 of G in competition with formation of OG. Both OG and Fapy-G stem from the same hydroxyl radical adduct, 8-OH-G$^{\bullet}$, which is subsequently either oxidized by one-electron to form OG or reduced by one-electron to form Fapy-G. Further elaboration can then build the additional 6-membered rings of the flavin.

We propose that the pathway from G to OG/RU was a "teaser", a way to kick-start the evolution of related chemical pathways that might eventually lead to the present-day biosynthesis of an optimized flavin heterocycle. In this scenario, OG served as a primitive flavin with superior redox properties to G, Fapy-G, or other early intermediates in the present biosynthetic pathway. Additional exploration of the surrounding chemical landscape would be necessary to arrive at the best redox-active structure, namely, dihydroriboflavin. The close relationship of OG and Fapy-G as common products of radiation damage to G is an intriguing element of this hypothesis. OG would be the more obvious direction to take toward a redox-active base compared to Fapy-G (Figure 2), but Fapy-G ultimately opens up an easier route to chemical synthesis of the additional ring system of flavin.

Overall, the observation of catalytic photoinduced electron transfer by OG in DNA and RNA oligomers is a step toward conferring the redox chemistry necessary for metabolism in the RNA world. The involvement of photon-driven acid–base chemistry in the deactivation pathway of purine excited states also represents a fundamental component of primitive metabolism. Whether or not protection against UV damage in the RNA world was a driving force for chemical evolution of flavin dinucleotides is debatable, but clearly a transition from iron–sulfur redox chemistry to organic redox chemistry must have occurred in order for living systems to evolve. Flavin and nicotinamide dinucleotides form the basis of organic-based redox metabolism, and therefore, an abundant source of the heterocycles or their functional

equivalents must have been available. Once the heterocyclic portion of $FADH_2$ was at least partially optimized, a mechanism for its incorporation as a small functional unit would have been needed. Yarus proposes that the Initial Darwinian Ancestor contained 5′ diphosphate linkages to nicotinamide or flavin nucleosides as a way of conferring oxidoreductase activity to small ribozymes.[4] A future challenge is then to observe whether 8-oxopurines or other redox ribonucleotides can serve this function in minimal ribozyme assemblies.

Exploration of extraterrestrial organic molecules might help resolve questions about the molecular origins of flavins. The detection of purines in meteorites[16] and the search for polycyclic aromatic hydrocarbons on Mars[53] raise the possibility that flavin-like molecules may also be found. Whether these would be precursors to life, or products thereof, would be the next challenging question to address.

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BIOGRAPHICAL INFORMATION

Khiem Van Nguyen was raised in Vietnam and received his B.S. degree in Chemistry from Hanoi National University in 2005. He recently completed his Ph.D. studies in photoredox chemistry of DNA and RNA bases in the laboratory of Cynthia Burrows at the University of Utah.

Cynthia J. Burrows was trained in organic photochemistry with Prof. Stanley Cristol (University of Colorado), in physical organic chemistry with Prof. Barry Carpenter (Cornell University), and in supramolecular chemistry with Prof. Jean-Marie Lehn (Université Louis Pasteur). She has held academic appointments at the State University of New York at Stony Brook and at the University of Utah where she is Distinguished Professor of Chemistry. Her search for beneficial attributes of the redox activity of 8-oxoG was stimulated by her mother's query, "Don't you do anything besides damage?"

FOOTNOTES

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The authors declare no competing financial interest.

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