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News & views

Structural biology

Glimpses of a light-sensing receptor in action

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Intense, ultrashort X-ray pulses have been used to probe the extraordinary reactions that occur in a light-sensing receptor, resolving a biochemical conundrum.

It is essential for many organisms to be able to respond to light. Biological systems use photoreceptor proteins to detect light through molecules known as chromophores. The bacterial photoreceptor CarH uses a vitamin B_{12} derivative called adenosylcobalamin (AdoCbl) as a chromophore, co-opting it from its normal function as a cofactor for enzymatic reactions[1,2]. Writing in *Nature*, a collaboration of several international teams of scientists (Rios-Santacruz *et al.*[3]) report that they have used cutting-edge structural-biology methods to capture snapshots of CarH in action, thereby revealing what happens to AdoCbl as soon as 10 nanoseconds after exposure to light. The findings answer a long-standing question about how CarH controls the light-induced breakdown of AdoCbl.

Light is a double-edged sword. On the one hand, it powers photosynthesis, the process that produces sugar to eat and oxygen to breathe. But on the other hand, light generates compounds known as reactive oxygen species (ROS), which can damage DNA. Organisms have evolved defence mechanisms to combat ROS, including ROS-neutralizing molecules called carotenoids. CarH regulates the biosynthesis of carotenoids in various microorganisms, ensuring that these compounds are produced only when needed — that is, in the presence of light.

Previous work established that CarH binds to DNA in the dark, repressing expression of the genes that encode carotenoid-biosynthesis enzymes, but it dissociates from DNA in the light, switching on carotenoid production[1,2]. Crystal structures[4] of CarH determined in 2015 showed that the 5′-deoxyadenosine (Ado) group of AdoCbl acts as a molecular 'doorstop' in the dark, preventing dissociation of the photoreceptor from DNA. Light exposure cleaves the bond between the chromophore's cobalt ion (Co) and the 5′-carbon (5′C) atom of Ado, causing Ado to be lost from the chromophore. With the doorstop gone, CarH can undergo a change in conformation that leads to dissociation of the photoreceptor from DNA[4].

The discovery that CarH uses AdoCbl as a chromophore was a surprise[1,2,4]. AdoCbl was well known to scientists as an enzyme cofactor, used to initiate enzymatic reactions through generation of a 5′-deoxyadenosyl radical[5]. The sensitivity of AdoCbl to light was widely known in the field, but in the context of radical reactions, this property was viewed as a bug rather than a feature. But as the saying goes, 'one man's trash is another man's treasure', so perhaps it should not have been surprising that nature found a way to use the light sensitivity of AdoCbl to its advantage. Still, it was puzzling to find that nature had co-opted a radical-generating cofactor as part of a defence mechanism that protects against hydroxy radicals and other ROS species. Why fight fire with fire?

To account for this conundrum, it was suggested[4] that CarH must influence the chemistry of AdoCbl to prevent it forming a radical. This hypothesis was shown to be correct with the discovery that light irradiation of CarH produces a molecule called 4′,5′-anhydroadenosine, rather than the 5′-deoxyadenosyl radical species[6]. But this finding raised another question: how does CarH alter the light-induced decomposition of AdoCbl to form 4′,5′-anhydroadenosine? What was needed to answer this question was the ability

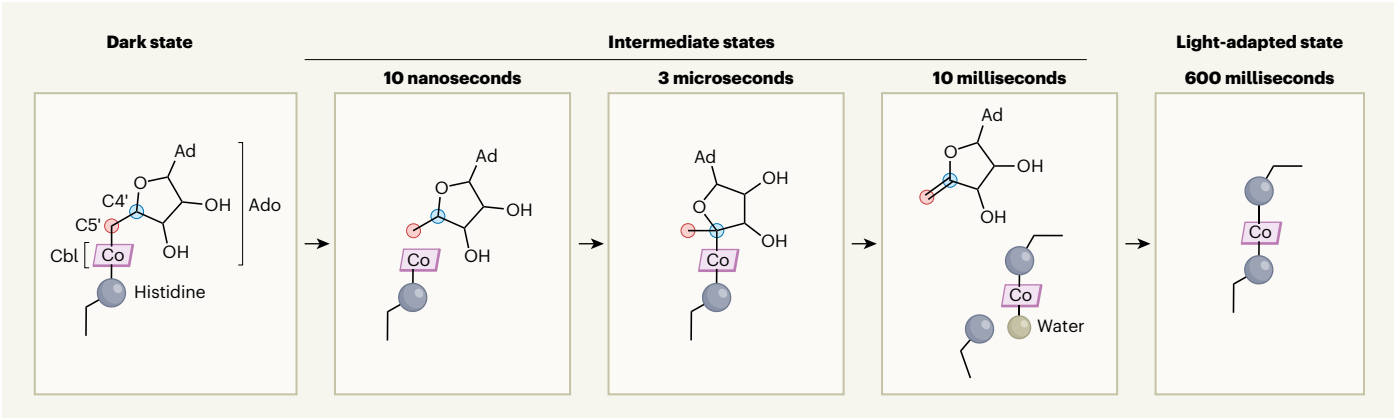

Figure 1 | Unexpected chemistry in a light-responsive receptor. The bacterial photoreceptor CarH senses light through a chromophore called adenosylcobalamin (AdoCbl), which consists of an organic component (Ado) attached to an organometallic component (Cbl, which contains cobalt; shown as a rectangular sheet viewed edge-on). Rios-Santacruz *et al.*[3] report X-ray structures of CarH acquired at various ultrashort times after activation by light. These structures capture intermediate states of CarH never observed before. The most striking intermediate forms within 3 microseconds and contains a cobalt–carbon bond involving the 4′-carbon of Ado, rather than the more typically bonded 5′-carbon. Grey circles, histidine amino-acid residues from the CarH protein. Ad, adenine, a nucleotide base. (Adapted from Fig. 1 of ref. 3.)

to 'see' intermediate states of CarH that form and decay quickly on light exposure, something that conventional X-ray crystallography cannot deliver.

Rios-Santacruz *et al.* have now overcome that problem using a technique called time-resolved serial femtosecond crystallography (TR-SFX). TR-SFX uses powerful light sources known as X-ray free-electron lasers (XFELs) to produce ultrashort, intense X-ray pulses that interact with protein microcrystals. Only one X-ray pulse is used per crystal, which prevents the protein from being damaged by the X-rays but still allows the protein structure to be obtained[7,8]. Using this method, the authors collected 'snapshots' of CarH at many time points after exposure to light, ranging from less than 10 nanoseconds to about 600 milliseconds (by which the time the final light-adapted state of CarH has formed). What they saw is remarkable.

The authors observed that the Co–C5′ bond of AdoCbl bound to CarH breaks within just 10 nanoseconds of illumination (Fig. 1). The bond breakage is accompanied by a protein conformational change that allows the cleaved Ado group to rearrange above the cobalamin (Cbl; the organometallic component of AdoCbl). Surprisingly, rather than leaving the protein, the Ado group reattaches to the cobalt ion of Cbl within 3 microseconds, but through a carbon atom adjacent to C5′ (the 4′-carbon, C4′), rather than through C5′ itself.

Cleavage of the new Co–C4′ bond would generate 4′,5′-anhydroadenosine, the product identified in an earlier study[6]. Rios-Santacruz *et al.* observed that this cleavage occurs after 10 milliseconds — the 4′,5′-anhydroadenosine has gone, and has been replaced by the side chain of a histidine amino-acid residue from CarH. This histidine residue binds to the top face of Cbl, whereas the bottom face is bound by a water molecule, temporarily displacing a previously bound histidine residue. After 600 milliseconds, the final protein rearrangement has occurred, yielding a structure in which there is a histidine residue bound to both the upper and lower faces of Cbl — the structure that had previously been characterized using conventional X-ray crystallography[4].

The formation of the Co–C4′ bond has a remarkable chemical effect: it prevents the release of a radical species that could damage DNA. The possibility that protein-bound Cbl groups can form carbon–cobalt bonds that are distinct from the typical Co–C5′ bond found in AdoCbl has been proposed previously[9,10], but the current study is the first to validate the existence of such a bond. The observations by this international group of authors expand the known chemistry of AdoCbl. This work also demonstrates the value of XFELs for answering biological questions.

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