Corrections and Retraction

CORRECTIONS

COMMENTARY

Correction for "Complex nature of malaria parasite hemoglobin degredation," by Daniel E. Goldberg, which appeared in issue 14, April 2, 2013, of *Proc Natl Acad Sci USA* (110:5283–5284; first published March 19, 2013; 10.1073/pnas.1303299110).

Due to a printer's error, the title appeared incorrectly. The title should instead appear as "Complex nature of malaria parasite hemoglobin degradation." The online version has been corrected.

www.pnas.org/cgi/doi/10.1073/pnas.1305990110

EVOLUTION

Correction for "Metazoan opsin evolution reveals a simple route to animal vision," by Roberto Feuda, Sinead C. Hamilton, James O. McInerney, and Davide Pisani, which appeared in issue 46, November 13, 2012, of *Proc Natl Acad Sci USA* (109:18868–18872; first published October 29, 2012; 10.1073/pnas.1204609109).

The authors note that Fig. 2 should have the following credit line: "Photo © NSW Department of Trade & Investment, Primary Industries Division artist Pat Tully."

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MEDICAL SCIENCES

Correction for "Primary aldosteronism and impaired natriuresis in mice underexpressing TGFβ1," by Masao Kakoki, Oleh M. Pochynyuk, Catherine M. Hathaway, Hirofumi Tomita, John R. Hagaman, Hyung-Suk Kim, Oleg L. Zaika, Mykola Mamenko, Yukako Kayashima, Kota Matsuki, Sylvia Hiller, Feng Li, Longquan Xu, Ruriko Grant, Alejandro M. Bertorello, and Oliver Smithies, which appeared in issue 14, April 2, 2013, of *Proc Natl Acad Sci USA* (110:5600–5605; first published March 15, 2013; 10.1073/pnas.1302641110).

The authors note that the affiliation "[b]Department of Integrative Biology and Pharmacology, University of Texas Health Science Center, San Antonio, TX 78229" should instead appear as "[b]Department of Integrative Biology and Pharmacology, University of Texas Health Science Center, Houston, TX 77030". The corrected author and affiliation lines appear below. The online version has been corrected.

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RETRACTION

BIOPHYSICS AND COMPUTATIONAL BIOLOGY

Retraction for "Voltage sensor ring in a native structure of a membrane-embedded potassium channel," by Liang Shi, Hongjin Zheng, Hui Zheng, Brian A. Borkowski, Dan Shi, Tamir Gonen, and Qiu-Xing Jiang, which appeared in issue 9, February 26, 2013, of *Proc Natl Acad Sci USA* (110:3369–3374; first published February 11, 2013; 10.1073/pnas.1218203110).

The authors wish to note the following: "The contrast of our final projection map was inverted, so that we interpreted the background density rather than the actual protein density in terms of structural features of the potassium channel-Fv complex. In addition, we indexed the 2D crystals with unit cell parameters of a = b = 175 Å, while the correct indexing would be a = b = 124 Å. Given these analysis errors, the resulting density map and our interpretation of the structural features are not correct. Accordingly, we would like to retract this paper. We acknowledge Yoshinori Fujiyoshi, Rod MacKinnon, Kazutoshi Tani, and Tom Walz for identifying the errors and pointing them out to us."

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COMMENTARY

Complex nature of malaria parasite hemoglobin degradation

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Hemoglobin degradation is a massive catabolic process that is essential for the intraerythrocytic development of malaria parasites (1, 2). This process takes place in an acidic food vacuole and is mediated by the concerted action of nearly a dozen proteases (3). The by-product of this degradation, free heme, is sequestered in a crystalline lattice called hemozoin (Fig. 1). The process of hemozoin formation has remained somewhat mysterious over the years. Under highly acidic conditions and high temperatures, hemozoin will form spontaneously (4). Using more physiological conditions, various proteins and lipids have been shown to accelerate the formation of hemozoin from heme (5–7). Chugh et al. have now advanced our understanding by linking the degradation and biomineralization processes (8). The authors show that there is a complex comprising many of the proteases and heme detoxification protein (HDP), the most potent of the hemozoin-forming proteins (7). Chugh et al. use a number of techniques to nicely show that this complex exists, and their case for protein–protein associations, in particular a submicromolar falcipain-2–HDP interaction, is compelling. The authors' functional characterization reveals that a collaboration of protease and HDP is required for substantial hemozoin formation from hemoglobin. This result is not surprising because hemoglobin is a stable molecule even at pH 5, and does not give up its heme easily, but the finding has never been formally demonstrated.

Chugh et al. (8) go on to show that chloroquine blocks association of falcipain-2 with hemoglobin and prevents hemozoin generation. At first glance, it would seem that blocking heme liberation through chloroquine action would counteract the ability of chloroquine to effect accumulation of nonsequestered heme, which is thought to be toxic to the parasite (9). It is possible, though, that if falcipain-2 is inhibited, the other proteases in the complex can still mediate liberation of heme but with less effective coordination with HDP. Detailed biochemical studies will be needed to sort out the mechanism of heme handling by the complex. Meanwhile, we still don't really know how chloroquine works (or artemesinin).

A number of other questions remain and some important ones are raised by Chugh et al.'s intriguing report (8):

First, what is the membership of the complex? With an estimated molecular weight of 200,000, there isn't room for all of the proteases identified by mass spectrometry. Some proteases may be variably present: for example, HDP, falcilysin, one plasmepsin, and one falcipain per complex. Alternatively, maybe these proteases are all present but some fall off during the preparation for molecular weight determination. Two important food vacuole proteases, plasmepsin I and dipeptidyl aminopeptidase I, were not identified in the pull-downs. Are they free-floating in the food vacuole or are they also part of the complex but not detected by the particular isolation procedure used? Another essential food vacuole protease, falcipain-3, did not associate with other members of the complex and did not pair with HDP to promote hemozoin formation from hemoglobin. Does this protease play a different role in the food vacuole? Does its essential role lie elsewhere in parasite biology?

Second, why is there a complex? Chugh et al. (8) show that proteolysis of hemoglobin before addition of HDP is just as good at hemozoin formation as preformed protease-HDP complex. The experiment was done with one protease added to HDP under one set of conditions. Perhaps follow-up experiments will show a kinetic advantage to having multiple components together. If the complex does make a difference, is it structured so that HDP is in position to take the heme as it is being liberated? Is there synergism between proteases in the complex? Are downstream proteases like falcilysin in

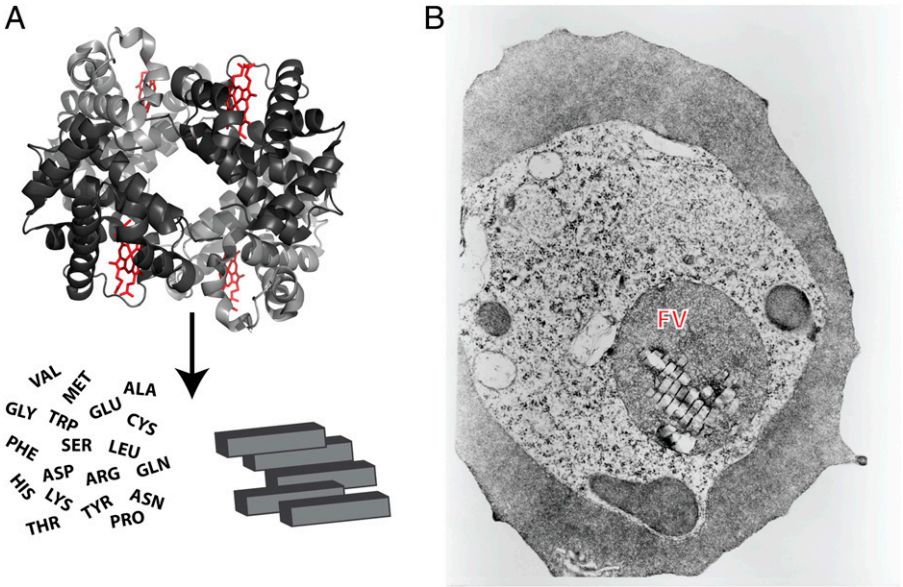

Fig. 1. *Plasmodium* hemoglobin degradation. (*A*) Hemoglobin is metabolized by a protein complex to free amino acids and crystalline hemozoin. Hemoglobin structure is from PDB ID 1GZX. (*B*) Transmission electron microscopy of a parasite-infected erythrocyte. FV, food vacuole. *Image reproduced from ref.* 12.

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See companion article on page 5392.

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position to receive peptide fragments from the initial proteolysis?

Third, where is the complex in the food vacuole? Is it on the membrane where lipids can help form the hemozoin crystals (10)? In lipid nanospheres (11)? Is it on the surface of the growing hemozoin once hemozoin formation gets started?

Finally, what should the complex be named? Perhaps the degradosequestrasome???

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