The FEBS Journal
FEBS PRESS science publishing by scientists
EDITORIAL

Do structures matter any more?

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It should be assumed that scientific publications that report macromolecular crystal structures do that for a reason, mainly to interpret the relationship of the analyzed biological or chemical phenomena to the structural data. This is indeed what would normally be expected to happen, but it is not exactly clear what to do if the structures themselves are defective in some significant way. Some errors in macromolecular structures (e.g., departures from the expected geometry if only the global fold of the macromolecule is relevant) may not invalidate other conclusions, but what should happen if the nature of the problem is such that major points made in the publication are impacted?

Two recent corrections of the published record made us consider the response of the authors and the journals to the deficiencies raised above. It was recently pointed out that three structures of the complexes of mouse kynurenine aminotransferase with presumed ligands (kynurenine, glutamine, and glycerol [1]), all bound in the active site of the enzyme, contained misidentified ligands [2]. Re-refinement of these structures utilizing structure factor files deposited in the PDB led to the conclusion that in all three cases the ligand was the same – a HEPES molecule from the crystallization buffer. This fact was pointed out to the Editor of the journal *Molecular and Cellular Biology*, and the authors of the original publication agreed with the suggestion regarding the identity of the ligand. In a recently published correction, the authors say that 'Although soaking the crystals with glutamine (the enzyme's best substrate) and kynurenine changed the protein cofactor form (from LLP to PMP) in our study, the enzyme active centers were predominantly occupied by HEPES molecules in the structures. These corrections do not impact the other conclusions of the paper regarding the functional effects of amino acids, pH, and temperature on mKAT III activity' [3].

The second example is the paper entitled 'Hydrogen bonds are a primary driving force for *de novo* protein folding' [4]. In that paper, the authors described their detailed studies of protein folding, using as their test case activation-induced cytidine deaminase, 'one of the most difficult proteins to obtain'. Their folding experiments were followed by the determination of the crystal structure of the refolded enzyme (PDB ID 5w09). Unfortunately, however, readers of their manuscript realized that the protein that was actually crystallized was the well-known *Escherichia coli* protein Hfq (PDB ID 2Y90), a common contaminant of recombinantly produced proteins. This discovery led to the withdrawal of the original publication and the coordinates were obsoleted in the PDB. However, the withdrawal note carried the following statement: 'Our conclusions regarding the critical role of proline residues in protein folding, successful folding of proteins at high pH, and hydrogen bonds as a driving force in *de novo* protein folding are not affected, and further details will be published elsewhere' [5].

What should we conclude from these examples? In the case of kynurenine aminotransferase, the original publication is still considered to be valid, thus indicating that the presence of the correct structures must have been completely irrelevant to any and all conclusions reached by the authors. That begs the question of why these structures were there in the first place, if their removal did not affect any of the results. In the case of the AID paper, it is a bit puzzling why the authors could claim that despite the fact that the wrong protein was crystallized, all other conclusion could still be supported. Could they be really sure that the protein whose folding behavior was being observed was truly AID? And even if it was, was it necessary to solve its structure?

We are well aware of the fact that it is cumbersome for the authors and for the journals to correct or retract published papers. At least in the examples given above the Editors were quite willing to correct the record, although their agreement to print the statements that the problems with the structures did not invalidate any other results raises the question of whether these structures should have been there in the first place. In some other cases known to us, the journal Editors never bothered to even answer critical comments about the published structures, or acted on the problems after more than a year. Maybe a better approach that would not indicate that the published defective structures were irrelevant would be simply retracting the papers without allowing the authors to

make the type of claims that were shown here. Of course, the best solution would be for the authors to make sure that the structures described in their papers are of high quality. Fortunately, that is almost always the case, but it would be good to change 'almost' to 'certainly' by more effective ways of removing rotten apples from the scientific literature.

Acknowledgements

This project was supported by the Intramural Research Program of the National Institutes of Health (NIH), National Cancer Institute, Center for Cancer Research.

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