Comment

Dog eat dogma

Gregory A Petsko

Address: Rosenstiel Basic Medical Sciences Research Center, Brandeis University, Waltham, MA 02454-9110, USA.
E-mail: petsko@brandeis.edu

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It is human nature to inflate one's ideas and contributions. It is also human nature to hang onto one's ideas long after they have outlived their usefulness, in much the same way that a parent will still support a child who has grown up to be a menace to society. Both traits are at work whenever a scientist makes sweeping statements. The more general one's insight or discovery can be claimed to be, the greater its seeming importance. And having gone out on that proverbial limb, a scientist will do much to avoid conceding that it may be less than it was thought to be, which is why so many outdated concepts have more lives than a cat.

Few statements in biology have been as sweeping as the 'Central Dogma of Molecular Biology': DNA makes RNA makes protein. Its name is always capitalized, like the Constitution of the United States or the Magna Carta. It is usually stated without qualification. It was referred to, from its inception, as a dogma rather than a theory. (Even Darwin had the modesty to call evolution a theory.) Scientists don't usually produce dogmas; that is nominally the province of religions, and even the briefest study of history will suggest that, in addition to admitting of no contradiction, dogmas tend to be accompanied by lots of other fun things, such as inquisitions and wars.

The Central Dogma was beloved of students because it was easy to remember and had no stated exceptions, like any good dogma. Sadly, it has fallen on hard times of late. The discovery of reverse transcriptase provided an inconvenient example of the synthesis of DNA from RNA. An attempt was made to re-establish dogma status by explaining that the phrase 'DNA makes RNA makes protein' really referred to the flow of genetic information, not the actual steps of synthesis. Then along came RNA editing, in which guide RNAs or enzyme action modify some messenger RNAs such that the final protein sequence cannot be deduced from the gene sequence alone. Alternative splicing didn't help either: it could be argued that it represents a case of RNA making itself, then making a bunch of different proteins. And then there was that inconvenient stuff about RNA catalysis, which suggested that there was once an RNA world in which RNA made protein without DNA getting into the act at all. To account for all this, the Central Dogma now would have to go something like this: 'DNA makes RNA makes protein, but sometimes RNA can make DNA and other times RNA makes RNA, which makes proteins different from what they would be if only DNA made the RNA, and once upon a time RNA made protein, probably, but no-one knows for certain'. Or, if you prefer your dogmas pithy: 'DNA makes RNA makes protein, except when it doesn't'.

Perhaps it is best to retire the Central Dogma, and before suggesting a replacement remind ourselves that, because it was a dogma, all of the exceptions – from reverse transcription to RNA catalysis to editing of the message – were initially dismissed as artifacts and had more trouble gaining acceptance than perhaps they should have from the quality of the experimental work. Skepticism in science is a good thing, but dogmas breed cynicism (which is not) and lead to reactionary thinking. Just ask Galileo.

Still, dogmas have their uses. Students, as stated earlier, find them very helpful. They provide a convenient encapsulation of the perceived wisdom of the moment. They are usually easier for lay people to understand than laboriously qualified statements. And they provide a clearly visible target for that most interesting breed of scientist, the iconoclast, to shoot at – rather like policemen's hats. So, I might as well suggest that genomics has a dogma that is more profound, I think, than the Central Dogma, and more robust to boot.

The Central Dogma of Genomics derives from structural biology. Concisely stated, it is: 'sequence determines structure determines function'. Chaperone-mediated protein folding does not violate this dogma, because chaperones do not induce in proteins a fold that is different from one

adopted when the proteins are allowed to fold on their own in dilute solution – chaperones just expedite the folding or prevent unwanted aggregation. Post-translational modification of the structure by limited proteolysis, phosphorylation, glycosylation and the like also does not violate the dogma, because the sequence and structure of the protein determine the nature of such modifications, and the sequence and structure of the protein after modification determines what the consequences of that modification will be. The dogma is vague about which sequence is referred to, which is useful because it forces us to think about it. Upon reflection, it is clear that the relevant sequence must be that of the protein, not the DNA or RNA, and specifically that of the protein following any modifications that may be made on the pathway to full expression of function. That is a very important conclusion, because it means the task of genome sequencing cannot be considered complete until genome-wide methods for detecting and characterizing changes in the protein sequence have been developed and applied.

The dogma asserts that it should be possible, ultimately, to deduce the function of a protein from its structure. Belief in the truth of this statement lies at the heart of structural genomics, which endeavors to determine structures for all of the gene products in a given organism. Yet here the dogma can be accused of oversimplification. Protein-protein interactions and protein localization within the cell can have profound influence on protein function. But I believe it is sound to argue in rebuttal that these things also depend directly on the sequence and structure of the protein in question.

The Central Dogma of Genomics is a concise summary of the basic assumptions that underlie this field. Though they are cast as a dogma, we would do well to bear in mind that they are only assumptions, albeit ones with good legs to stand on. If the seeds of eventual overthrow are sown anywhere, they may be in the word ‘function’. For, unlike most important words in science, function is a word whose meaning is highly situational. But that’s another column.