Reviewer #1: Review of Bilaterian evolution re-considered: aligning theory with fact

1. by James Graham

Despite the apparently axiomatic structure of this paper, it's surprisingly hard to pin down exactly what Graham's thesis is. I shall try to do so.

Graham begins by observing that each living multicellular creature is the consequence of many mitoses. Furthermore, each living multicellular creature had many multicellular ancestors; each living multicellular creature is the consequence of many multicellular mitoses that worked. So much, so self-evident. This must be true of all multicellular organisms: slime-moulds, volvocines, fungi, plants, jellyfish and elephants. Graham, however, is particularly interested in bilaterans.

He asserts that, in the course of bilateran evolution, natural selection must have selected devices that ensured the regular production of "perfect" adults. Setting aside the naÃ¯ve use of "perfect" I agree.

Specifically: "It is proposed that early Bilaterian populations experienced "cancer selection," - "the extermination, in evolutionarily significant numbers, of young animals (and their genotypes) that did not avoid imperfect mitosis leading to cancer." Again, I agree.

Cancer selection is the explans - explanation. But what is the explanandum - the thing to be explained?

That, as I said, is hard to pin down. I think it is the diversity and complexity of bilateran forms. "That early Bilaterian gene pools acquired masterful control over developmental mitosis is evident from their descendants' accomplishment: constructing those unbroken chains of precise development, in millions of diverse forms and many trillions of individuals, of the most complex things known to exist in the universe."

If so, the argument seems to be this: cancer selection resulted in devices that increased the precision of mitoses. Those permitted, in turn, the evolution of bilateran diversity. In current jargon, the mutations that resulted in those devices were "potentiating" mutations or, in older language "key innovations". Let's consider this claim.

Are anti-cancer devices necessary for the evolution of diverse multicellular bodies? Plainly this is not true in general. As Graham concedes, some multicellular creatures don't apparently get cancer. Plants and fungi don't. It's fairly clear why cancer selection can't have been an important force in plant and fungal evolution: plants and fungal cells have walls and are immotile. So should a plant can get a tumour in the sense of a local loss of proliferation control (e.g., a gall), that tumour will not metastasize and kill it. So, some other selective force must be responsible for the 200,000 + species of plants and millions of species of fungi.

Cnidarians are more problematic. Graham says that Cnidarians are immune to cancer. This may or may not be true, but let's accept it. Graham does not explain why Cnidarians are immune to cancer. But he grants that, for Cnidarians too, cancer selection cannot have played a role in their evolution. So, again anti-cancer devices are not necessary for the evolution of diverse

multicellular bodies. (Graham is inclined to be dismissive of Cnidarians - "Nothing but jellyfish." But it's worth pointing out that there are about 10,000 species of extant Cnidaria ranging from microscopic hydrozoans to metre-sized Cubomedusans.) In any event, by Graham's argument, some other selective force must be responsible for all those Cnidarians. So, we have at least three taxa - plants, fungi and Cnidaria - that embrace many diverse forms and which have not experienced the driver of cancer selection, that is, they evolved by just regular kinds of natural selection.

All this is just a recapitulation of Graham's argument as I understand it. And it exposes its weakness: if other taxa can evolve thousands of diverse forms, and the mitotic regulatory devices that they require - and can do so without cancer selection, why, then, do we need to invoke cancer selection to explain bilateran diversity? For that is exactly what he seems to believe: "Lethal juvenile cancer seems to be the only observable phenomenon that could have led to the imposition of an imperative of precise developmental mitosis." [in the bilateria]

But why? All organisms need to build functional organs. The development of a worm's pharynx, a finch's beak, an elephant's trunk, must all be under severe control (i.e., the mitoses that make those organs must be strictly controlled) if they are to develop into functional organs. So must the primrose's petals and a hydra's tentacles. Mutations that disrupt the developmental patterns - the precision of the mitotic control - will be selected against. (And there's an abundance of evidence for this.) This will be true even if the mutations merely result in a disproportion in size or shape rather than a tumour. This seems to suffice to explain the precision of mitotic control - and Graham has given us no reason to think otherwise.

Now, I do believe that cancer selection, a particular form of natural selection, was important in metazoan evolution. I think that many cellular features (tumour repressors to stem-cell niche architecture) are the result of selection for cancer resistance. I believe this because I read Graham's book. But I see no reason to suppose that such features are the cause rather than the consequence of bilateran diversity driven by quite conventional kinds of natural selection. Or, to put another way, I think that cancer resistance was necessary but not sufficient for the evolution of bilateran diversity.

The fact is that Graham's argument, as I understand it, is just one of many possible ideas that purport to explain the success of the Metazoa or the Bilateria. Some say that the invention of Collagen was the potentiating factor; others point to micro-RNAs or Hox genes or MHC-mediated immunity. All these arguments have the same form: Bilaterans are diverse and Bilaterans get cancer (have Hox genes, Collagen etc.); therefore Bilaterans are diverse because they get cancer (have Hox genes, Collagen etc.). The non-sequitur is plain. To the degree that they invoke historically unique events (the evolution of the Bilateria) they are quite unfalsiable.

Which brings me to his proposed tests. Some are logically incoherent (e.g., Initiate lethal cancer in a Bilaterian without using a mutagen or a mitogen. But cancer is excessive cell proliferation, so anything that causes it is, by definition, mitogenic.) Indeed, of the various tests that Graham proposes to falsify his theory, only the first seems remotely germane: Using a mutagen, initiate lethal cancer in a jellyfish or other non-Bilaterian multicell.

Let me give it a shot. Cancers are "selfish cell lineages". Mutations that cause selfish cell

lineages occur all the time in the slime mould Dictyostelium and are deleterious (I am not sure if they are lethal - they do prevent sexual reproduction). Dictyostelium has evolved genetic defenses against this. That's a slime-mould version of cancer selection. But slime moulds are (to paraphrase Graham) "just slime moulds".

But actually, I think that this whole argument about Cnidarians is misconceived. The real puzzle is why don't Jellyfish get cancer? Graham, oddly, just seems to accept the absence of in Cnidarians as an inexplicable, brute, fact. Yet Cnidarians have motile cells and must get potentially oncogenic mutations like everything else. The first answer is that I suspect that if one kept lots of jellyfish in the lab you'd find that they do get cancer. The only commonly kept Cnidaria are Hydra and Nematostella. But they're really small and the risks of cancer in very small animals are small, so one may have to really look at lots of them. Alternatively, perhaps they have really good cancer defenses since, as adults, they have totipotent stem cells.

I don't have the answer to this - but this brings me to my final point. Instead of pushing this rather dubious global theory of bilateran evolution, I'd much rather Graham focused on asking: why do some animals get cancer and others don't? Just this week Nature published a paper on cancer resistance in naked mole rats - fascinating and entirely predicted in terms of Cancer Selection.

http://www.nature.com/nature/journal/vaop/ncurrent/full/nature12234.html

Or, if he wants to focus on the putative Cnidarian / Bilateran difference, talk to some cell biologists working on p53 function in Nematostella

http://www.plosone.org/article/info%3Adoi%2F10.1371%2Fjournal.pone.0000782

Or regeneration in Hydra

http://www.sciencedirect.com/science/article/pii/S0012160606014308

And try to come some understanding of what, if anything, is the critical difference between Cnidaria and Bilateria.

Graham has done us a service in drawing attention to cancer selection as a selective force. But there's just no reason to believe that it is the selective force that has shaped the diversity of the Metazoa. And the argument that it did so is so thin that's it's just not worth publishing.