Somatic evolution of metabolic reprograming: mutation limited or selection limited?

Intended for

Matters Arising

In response to

Khandelwal and Sharma (2026) Understanding the somatic evolution of metabolic traits. *Nature Metabolism* https://doi.org/10.1038/s42255-026-01551-7

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Abstract:

Somatic mutations can potentially be responsible for metabolic reprogramming, but the crucial question is whether the evolution would be mutation limited or selection limited. Mathematical and statistical considerations make the case for selection limited evolution stronger, e.g. somatic evolution of cancer is shown to be selection limited than mutation limited. Although some insights are developing into the selection on cancer causing mutations, we have no idea how selection might work on mutations altering metabolic regulation. Therfore the argument for metabolic reprogramming by somatic evolution is only a speculation at present and a focus on selection mechanisms can only make it stronger.

The idea that somatic mutations contribute to metabolic reprogramming[1] is an interesting possibility which needs a critical look from an evolutionary perspective. The idea appears qualitatively sound but quantitative thinking exposes potential flaws. If somatic mutations (including mtDNA) have to lead to significant heteroplasmy or affect metabolic regulation, the mutant cells need to be there above a threshold proportion among the cells involved. The methods of detecting heteroplasmy have lower limits of detection of about 1% [2]. A much higher proportion of mutant cells would be needed for bringing about a detectable change in the net metabolic behavior. The normal frequency of mutations is of the order 10^{-8} per nucleotide per generation [3]. If the fate of the mutant cell is not different from other cells, i.e. no selection acting on them, they will remain in the same proportion on an average. Reaching the threshold proportion by chance alone has a very small probability. Hence, reaching the threshold proportion by mutation alone is unlikely unless the mutants have some selective advantage in the adult stem cell (ASC) population. Increasing the mutation rate to 1 in 100 or 1 in 1000 is not the solution because it will lead to error catastrophe. The authors mention adaptive directed mutations without discussing them in details. The existence of such a phenomenon is claimed many times [4] but is restricted to a few specialized examples and remains controversial. Even if we accept directed mutations, its reported frequency is still not large enough[5] to explain heteroplasmy or metabolic reprogramming in the absence of any selection. Also, whether the ability to carry about direct mutagenesis (if present) offers any long-term evolutionary advantage is debated [6].

If reprogramming is to be achieved by mutants, a mechanism for the mutant cells to get a selective advantage over other cells should exist by which they can grow to a significant proportion to bring about any effective reprogramming. Since selective forces are shaped by the tissue microenvironment [7,8], it is more likely that stress or altered contexts modify tissue microenvironments and thereby differentially select the mutants. In contrast, it is unlikely that stress increases the mutation rates so much that detectable heteroplasmy would result without accumulating other deleterious mutations.

For somatic evolution, mutations need to happen in ASCs. Mutations in differentiated cells would vanish soon since most differentiated cells undergo senescence and die. We understand very little about selection upon mutants within ASC population. A mutant being metabolically adaptive for the organism is not a sufficient reason for the mutant to get

selected. It needs to get a specific relative advantage over other competing cells among the ASC population. Only recently we have some insights into how context dependent selection might work on somatic mutants [7–10] . These selective forces should be at the center of thinking for the Khandelwal and Sharma [1] hypothesis to be theoretically sound.

Currently we do not know anything about such mechanisms even speculatively in the context of metabolic reprogramming. While Khandelwal and Sharma [1] are certainly not averse to the concept of selection, they have cited some references to it [10] (for other potential examples mentioned in the paper i.e. “PNAPLA3-I148M mutation….. polygenic risk scores for statin therapy, APOE ε4 and anti-amyloid drugs, TCF7L2 variants in GLP1 receptor agonist-based therapy”, appropriate citations seem to be missing), they still appear to think that increased mutation rates and possibly directed mutations are central to somatic evolution.

The question which evolutionary processes are mutation limited and which ones are selection limited needs to be central to the biology of somatic evolution. The number of stem cell divisions in the human development and lifespan are orders of magnitude greater than average mutation rates [11,12]. Therefore, the availability of any specific mutant for selection to act is unlikely to be limiting in somatic evolution. Increased rates of mutations or directed mutations are neither necessary nor sufficient for somatic evolution. Cancers that were thought to be mutation limited for a long time, are now shown to be selection limited [11,13–15]. Parallel to cancers is the case of evolution of viral variants during an epidemic. Classically believed to be mutation limited, it is now argued to be selection limited [16,17]. Therefore, the possibility of metabolic reprogramming by somatic evolution needs to be viewed carefully. If it is true, the possible mechanisms of selection need to be at the center of the thinking, not stress driven or directed mutations. Context dependent selection is the key to somatic evolution, if any.

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