

Colon Cancers Get a Negative (Selection) Attitude



A key concept in cancer genomics research is the idea that we can apply lessons learned from evolutionary biology to the study of tumorigenesis. If we consider the host as a challenging environment or niche, and the tumor as a sort of pseudospecies that thrives or dies out on the strength of individual transformed cells' success within this environment, we can leverage evolutionary models to understand the importance of mutational events that contribute to tumor growth. This has aided in the identification of driver mutations that appear in cancer genomes at higher frequency than could reasonably be expected by chance.

There is, however, a conceptual twist to the parallels between evolution and carcinogenesis. Natural selection can include both positive selection (enrichment for traits that provide a selective advantage) and negative selection (elimination of deleterious mutations/traits). Curiously, although species evolution uses both mechanisms (and often relies heavily on negative selection), studies to date have suggested that selection of somatic mutations in tumors is driven almost entirely by positive selection.

A new study from Jonchere et al¹ at INSERM challenges this paradigm. In their article, featured in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, they present whole-exome sequencing data from a cohort of colorectal tumors with microsatellite instability (MSI). By analyzing these data with predictive modeling algorithms, they found clear evidence for negative selection (ie, mutations detectable at much lower frequencies than predicted by stochastic baseline rates) of somatic mutation events in repetitive microsatellite sequences.

As in previous studies in the field, Jonchere et al¹ did not, for the most part, observe negative selection in nonrepetitive sequences, and other than a few rare coding sequence mutations the events were largely in long noncoding repeats within 5' and 3' untranslated regions. Furthermore, re-analysis of MSI tumors in an available The Cancer Genome Atlas data set confirmed the observations. Thus, it may be that the dearth of negative selection events found in previous studies is owing to a previous focus on nonrepetitive sequences, although the specifics of why negative selection preferentially would target repetitive sequences need more exploration.

Jonchere et al¹ knocked down some of the genes preserved by negative selection (*WNK1*, *HMGXB4*, *GART*, *RFC3*, and/or *PRRC2C*) and showed that this resulted in enhanced apoptosis, reduced proliferation, and impaired xenograft growth of SW480 or HCT116 cells. Although negative selection in coding regions was relatively rare, these experiments nonetheless provide proof-of-concept data that some negatively selected events can influence tumor cell biology.

Surprisingly, although these mutations had acute negative effects on tumor cells, they also had a paradoxical association with worse outcome in patients. Either alone or in aggregate, the negatively selected coding region mutants identified by Jonchere et al¹ were associated with significantly shorter disease-free survival. It is not clear whether the same will be the case for the majority of noncoding mutations, which likely will require larger cohorts to test effectively.

Together, the data from Jonchere et al¹ pose an interesting conundrum. The article provides clear evidence that negative selection occurs in colorectal cancer (CRC), or at least in MSI CRC. However, the subset of negatively selected mutations that lie in coding regions appear to have paradoxical effects on tumor cell fitness vs host survival. Unfavorable (to the tumor) mutations could in principle simply be overcome by high genetic instability and positive selection in tumor evolution, but that would not explain the association with actually shorter survival curves. Thus, as Jonchere et al¹ proposed, there must be other compensatory mechanisms. Future studies uncovering these mechanisms potentially could define a previously unappreciated fundamental process that helps drive MSI CRC carcinogenesis.

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Reference

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Conflicts of interest

The author discloses no conflicts.

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