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Perspective

Mutagenesis Caused by Single-Stranded DNA Protonation

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INTRODUCTION

Mutagenesis is random in the sense that the occurrence of each mutational event cannot be predicted precisely in space or time. However, when a big enough number of mutations are examined, recurring patterns of base alterations known as mutational signatures can be detected. To date, 60 single base substitution signatures (SBS) have been generated from cancer genomics data analysis. We recently discovered that the ubiquitous signature SBS5 matches the pattern of Single Nucleotide Polymorphisms (SNPs) in humans and has analogues in a variety of other animals. We have demonstrated that a comparable mutational trend in yeast is based on error-prone Trans Lesion DNA Synthesis (TLS) and glycolytic sugar metabolism using a temperature sensitive single-Stranded DNA (ssDNA) mutation reporter system.

We explored the impact of experimental manipulations on pH and mutagenesis because glycolysis is known to produce excess protons. We hypothesized that yeast metabolizing 8% glucose would release more surplus protons than 2% glucose cells. Cells metabolizing 8% glucose had lower intracellular and extracellular pH levels, which was consistent with this. Similarly, removing vma3 (which codes for a vacuolar H^+ ATPase subunit) enhanced mutagenesis. We also discovered that cultivating cells in low pH medium or treating them with edelfosine (which makes membranes more permeable to protons) boosted mutagenesis.

DESCRIPTION

The mutational pattern caused by 20 M edelfosine treatment resembled the SBS5-like TLS and glycolysis-dependent mutational patterns previously described in ssDNA. Overall, our findings correspond with many biochemical investigations that suggest that protonation of nitrogenous bases can change base pairing and stabilize some mispairs, shedding fresh light on a common type of intrinsic mutagenesis.

Mutations are the raw material for natural selection evolution. Mutations frequently occur as a result of DNA damage caused by either endogenous mechanisms or external exposures. Endogenous DNA damaging processes include cytosine or 5-methylcytosine deamination to uracil or thymine, respectively; base oxidation; base alkylation; glycosidic bond breakage; single- and double-stranded DNA breaks. Aflatoxin, aristolochic acid, ionizing radiation, tobacco and UV light are all examples of exogenous DNA damage. Base pairing features can also be altered by spontaneous ionization or isomerization (*i.e.,* tautomerization) of DNA bases, which is regarded to be another probable source of mutations.

It is important to highlight that these and other DNA-damaging processes or exposures do not uniformly impact all bases. Each of the four bases in DNA, adenine, cytosine, guanine and thymine, has its own set of reactive chemical groups (amines, carbonyls and labile ring atoms). The local sequence context can also influence susceptibility to DNA damage. As a result, any particular DNA damaging process or agent may be more likely to react with one or more bases than others, resulting in recurrent, reproducible patterns of sequence changes known as mutational signatures.

The Non-negative Matrix Factorization (NMF) approach is commonly used to extract mutational signatures from genomic data sets. At this time, the Catalogue of Somatic Mutations in Cancer (or COSMIC) describes roughly 60 Single Base Substitution (SBS) signatures.

Despite significant advances in understanding the aetiologies of mutational signatures, one of the most common remains largely unknown. SBS5 is identified in all cancer types and almost all individual cancer samples and is often one of the most significant signatures in each sample. The number of SBS5 mutations increases steadily as we age; nevertheless, there is significant diversity in the magnitude

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of this "clock-like" mutation accumulation effect between individuals, *i.e.,* some have many SBS5 mutations while others have few. Furthermore, the SBS5 pattern fits over 70% of mutations in early human embryos and 75% of de novo mutations in human infants.

Unlike other mutational signatures, which may decline in incidence when malignancies undergo sub clonal diversification, SBS5 is usually a dominant signature that contributes significantly to intra tumor heterogeneity. Indeed, the pattern of human Single Nucleotide Polymorphisms (SNPs) substantially resembles that of SBS5. We have shown that a similar mutational pattern can be reproduced using a baker's yeast (Saccharomyces cerevisiae) reporter system with regulated synthesis of genomic single-Stranded DNA (ssDNA). The SBS5-like mutational pattern is driven by error-prone trans lesion DNA synthesis in ssDNA and sugar metabolism areas. When cdc13-1 cells are arrested in the G2 phase of the cell cycle on medium containing higher glucose, they exhibit greater SBS5-like mutagenesis.

Furthermore, we demonstrated that inhibiting glycolysis completion with an auxin-inducible degron mutant of the main pyruvate kinase gene prevents 90% of SBS5-like mutagenesis.

Mutation frequency assays

Single colonies were inoculated separately into 5 mL of YPDA-based liquid rich medium in round bottom glass tubes to begin mutagenesis experiments. For the 2% *vs.* 8% glucose studies, each colony was suspended in a tiny volume of sterile water before being inoculated into each media type in equal aliquots. For three days, cells were cultivated at 200 RPM at a permissive temperature (23°C). The cultures were then diluted 1:10 into fresh media in new glass tubes, transferred to a restricted temperature (37°C) and gently agitated at 150 RPM for six or 24 hours.

Cells were collected, lightly centrifuged, washed in water and plated onto synthetic complete media to assess survival and onto canavanine containing media with 0.33 adenine to select for mutants (CanR colonies were off-white, while CanR Ade colonies turned into red or pink). Because the cells were so delicate after the temperature adjustment, they were handled very cautiously. This plating process was previously reported in detail. The synthetic complete and canavanine plates were incubated for five days at 23°C.

Single colonies were injected individually into 5 mL of YPDA (2% glucose) in round bottom glass tubes for experiments comparing chemical treatment *vs.* mock-treated controls and cultured for three days at permissive temperature at 200 RPM. The cultures were then diluted 1:10 into fresh media in fresh glass tubes, with or without the test chemical and shaken gently at 150 RPM for 24 hours.

CONCLUSION

We investigated the mechanisms that contribute to intrinsic background or spontaneous mutagenesis inside ssDNA areas in a budding yeast model system, *i.e.,* mutagenesis that occurs without the addition of a mutagen. We recently demonstrated that the resulting mutational pattern matched COSMIC SBS signature. Many biological systems have analogues of these comparable mutational patterns. Furthermore, the pattern of human SNPs is nearly identical to that of SBS5. Given the pervasiveness of this set of linked mutational patterns, we reasoned that any underlying aetiology is likely to be tied to an endogenous process or agent that is well preserved and that many biological systems are routinely exposed.