Error-prone bypass of pre-existing damages during the replication of the lagging strand is substantial source of mutations in cancers and germline

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Approach, predicting preferential fork direction applied to cancers, shows that discontinuous synthesis of the lagging strand is the main source of single stranded DNA attacked by APOBEC and demonstrates that mismatch repair system is more efficient on the lagging strand compensating for more errors on it[1–4]. Detailed description of replicational and transcriptional asymmetries in human polymorphism for 6 mutation types with account for adjacent nucleotides contexts (96 mutation types overall) shows that transcriptional and replicational asymmetries are correlated for each context. Such relation may emerge if damages preferentially affect only one of two complimentary contexts, making this context more mutable. Damages, eliminated from the transcribed strand, lead to the transcription asymmetry, also damages may be converted into mutations on the lagging strand more frequently, causing the replicative asymmetry. We found that in cancer samples with dominance of UV-induced, smoke-induced and liver cancer specific mutational patterns mutations are biased both toward non-template and lagging strands. Moreover, UV-damages are observed more frequently on the lagging strand in UV-irradiated cells and asymmetry of damages between leading and lagging strands increases with the time after irradiation. At last, we describe few intergenic regions that have strong bias toward one of the strands for UV-induced or for liver cancer-specific mutations. Two longest starches of DNA with mutational asymmetries, found in melanoma and liver cancer (one each), also have asymmetry for smoke-induced mutations and for population polymorphism. Mutations in these regions tend to occur on the lagging strand. Moreover, cancer samples with polymerase ε, lacking the exonuclease activity and accumulating most mutations due to replicative mismatches, show strong and concordant mutational asymmetry. Therefore, there are many lines of evidences that pre-exiting damages have higher probability to be converted to mutations during the replication of the lagging strand when compared to the leading strand and this process has substantial contribution to mutagenesis in cancer and in germline.