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Research Article

DNA REPLICATION OUTSIDE OF S PHASE IN CANCER CELLS COULD BE DNA-TO-DNA TRANSCRIPTION

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Abstract

Recently, literature search showed that cancer cells often have DNA replication outside of S phase. This DNA replication can occur during G2, M, next G1 phases of the cell cycle, which seems to have missed up the subdivision of standard cell cycle. We don't believe that there is DNA replication machinery in every phase of the cell cycle. We assume that instead of DNA replication outside of S phase, DNA-to-DNA transcription could be a real thing that was first found in malaria parasite *Plasmodium falciparum*. Besides, both cancer cells and malaria cells belong to eukaryotic cells and have common feature of uncontrolled cell division; therefore, if there is DNA-to-DNA transcription in malaria cells, the cancer cells should have this function too. DNA-to-DNA transcription might not miss up the subdivision of the cell cycle and might help to resolve various replication stresses encountered in DNA replication during the S phase and preserve the genome integrity.

Keywords: DNA Replication Outside of S Phase, DNA-to-DNA Transcription, *Plasmodium falciparum,* Cancer Cells, Cell Cycle.

INTRODUCTION

In 2016, we first proposed that DNA-to-DNA transcription might exist in eukaryotic cells, which is based on experimental findings from the study using malaria parasite *Plasmodium falciparum* [1] [2]. We posit that CAGFs were single-strand DNA (ssDNA) and produced outside of S phase. Besides, like fluctuation in cyclin levels during cell cycle progression, these CAGFs were amplified and degraded at different points of the cell cycle, indicating that they are regulating cell cycle progression, which are quite like some RNA functions， this is the reason why we proposed that CAGFs was derived from DNA-to-DNA transcription, and why we had not named this phenomenon as DNA replication outside of S phase. Based on biological sciences, the term transcription mainly refers to DNA-to-RNA transcription. To explain the mechanism of DNA-to-DNA transcription, we proposed a hypotheses of endonuclease dependent cutout [3]. To provide convenience to people who want to repeat our experiment, we have published DNA sequences of two specific primers (SP1 and SP2) for PCR application [1]. Unfortunately, after 10 years, no people have repeated this experiment and no articles reporting the results of DNA-to-DNA transcription research. Recently, literature research showed that cancer cells often have DNA replication outside of S phase [4][5][6], which makes us think that cancer cells might have DNA-to-DNA transcription. In this paper, a theoretical exploration of the possibility of DNA-to-DNA transcription in cancer cells is presented.

DNA-TO-DNA TRANSCRIPTION MIGHT EXIST IN CANCER CELLS

DNA-to-DNA transcription was proposed based on experimental findings from research using malaria parasite *Plasmodium falciparum* [1]. There are some commonalities between malaria cells and cancer cells. Both of them belong to eukaryotic cells and have uncontrolled cell division. Besides, many antimalarial drugs have anticancer effects.

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Malaria cells produced CAGFs outside of S phase and therefore, we assume that like malaria cells, cancer cells might have DNA-to-DNA transcription. Due to various replication stresses [7], cancer cells have under-replicated DNA regions during S phase, and therefore they have DNA replication outside of S phase. Based on the results of few papers, this DNA synthesis can extend into G2, M, and even G1 phase [4][5][6][8], indicating that every phase of the cell cycle (from G1 to M) has DNA replication. This type of DNA replication might not be true because it indicates that every phase of the cell cycle should have DNA replication machinery and if this machinery works, the functions of G1, G2, and M phases will be interfered, which seems to have messed up the subdivision of the cell cycle. The standard cell cycle includes G1 phase that is preparing for entry into S phase; S phase (DNA synthesis) conducts DNA replication for entry into G2 phase; G2 phase is preparing for entry into M phase; M phase (mitosis) conducts cell division, distributing chromosomes into two identical new cells. This subdivision is not only observed by microscopy but is also genetically determined, which suggests that DNA replication outside of S phase might not exist in cancer cells and as such, it cannot really mess up the subdivision.

Some researchers have argument about mitotic DNA synthesis (MiDAS) because they are not clear how MiDAS is coordinated with chromosome in mitosis and how a newly synthesized DNA is reassembled into a correct chromatin state [5][9]. Overall, DNA replication outside of S phase in cancer cells may not be a real DNA replication. Instead, we assume that DNA-to-DNA transcription could be a real thing， which produces ssDNA transcripts (such as CAGFs) that might regulate cell cycle progression and resolve the DNA replication stresses encountered in DNA replication [1]. The DNA-to-DNA transcription may occur during G1, S, G2, and M phases. The ssDNA accumulation in the cytoplasm of cells is an indirect support for existence of DNA-to-DNA transcription in cancer cells [10] [11]. DNA damage-driven R-loops enhance the active release and buildup of ssDNA in the cytoplasm of cells [12], which supports DNA-to-DNA transcription and our hypothesis of endonuclease dependent

cutout [3]. Most importantly, the ssDNA fibre from the R-loop, which would be more susceptible to the action of nucleases and genotoxic drugs [13], indicating that the ssDNA fragments will be released from R-loops. Chloroquine that is genotoxic drug could induce CAGFs in *Plasmodium falciparum* [1], which is similar to the nature of R-loops with an RNA-DNA hybrid and a displaced ssDNA. If displaced ssDNA fragments or newly synthesized ssDNA fragments of about 100-2000bp are circularly released from R- loops, the existence of DNA-to-DNA transcription in cancer cells could be completely proved. Therefore, study of R-loops is vitally important for proving DNA-to-DNA transcription. Other locations for researching DNA-to-DNA transcription might be DNA-to-RNA transcription bubble because DNA replication initiation and termination are coupled to RNA transcription in human cells [14], and DNA replication-transcription conflicts [15]. Compared to DNA-to-RNA transcription, DNA-to-DNA transcription might be unnoticeable. The transcripts produced from DNA-to- DNA transcription are ssDNA fragments and DNA polymerase used in DNA-to-DNA transcription may be different from that used in DNA replication. DNA replication outside of S Phase and DNA-to-DNA transcription are summarized in Figure 1.

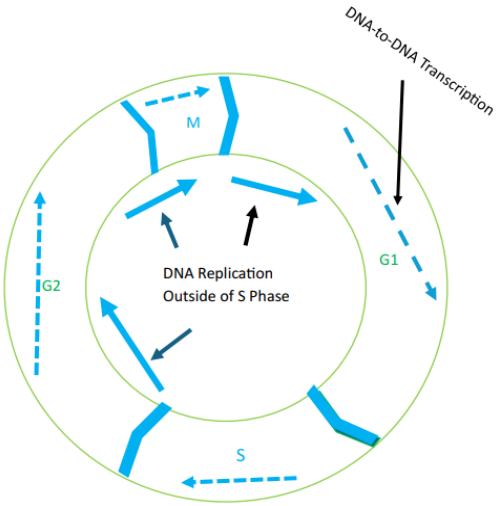

Figure 1. Cell-cycle phases of DNA replication outside of S phase and DNA-to-DNA transcription. Any phases where there are so-called under-replicated DNA regions will have DNA replication outside S phase. Any phases where there are DNA-to-RNA transcription bubble, R-loops and the regions of DNA replication-transcription conflicts might have DNA-to-DNA transcription that is difficult to detect

CONCLUSION

DNA-to-DNA transcription was proposed 10 years ago, but till now, no research about DNA- to-DNA transcription has been reported. The reason is that DNA replication may interfere the study of DNA-to-DNA transcription. We think that investigation of the origin of ssDNA fragments in eukaryotic cells is crucially important, especially in the phases outside of S phase. Recent literature reporting DNA replication outside of S phase in cancer cells attracts our attention because we don't think that this DNA replication is a real DNA replication and instead, it could be DNA-to-DNA transcription that might happen during all phases of the cell cycle. Besides, cancer cells and malaria cells have some common features, it is possible that cancer cells may have DNA-to-DNA transcription. R-loops can release ssDNA fragments that can be induced by genotoxic drugs, which is assumed to be an example of DNA-to-DNA transcription in eukaryotic cells. Conclusively, further exploration of DNA-to-DNA transcription is fundamentally important in the study of genome functions, the results of which may contribute to development of biotechnical methods for treatment of cancer and other diseases.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

REFERENCES

1. Li, G.D. (2016) Certain Amplified Genomic-DNA Fragments (AGFs) May Be Involved in Cell Cycle Progression and Chloroquine Is Found to Induce the Production of Cell-Cycle-Associated AGFs (CAGFs) in *Plasmodium falciparum*. *Open Access Library Journal*, 3, e2447.
2. Li, G.D. (2016) DNA to DNA Transcription Might Exist in Eukaryotic Cells. *Open Access Library Journal*, 3, 1-4.
3. Li, G.D. (2016) A Possible Mechanism of DNA-to-DNA Transcription in Eukaryotic Cells: Endonuclease Dependent Transcript Cutout. *Open Access Library Journal*, 3, 1-4.
4. Ovejero, S., Bueno, A., Sacristán, M.P. (2020) Working on Genomic Stability: From the S- Phase to Mitosis. *Genes (*Basel),11(2):225.
5. Bhowmick, R., Hickson, I.D., Liu, Y. (2023) Completing Genome Replication Outside of S Phase. *Mol Cell*,83(20):3596-3607.
6. Bournaka, S., Badra-Fajardo, N., Arbi, M., Taraviras, S, Lygerou, Z. (2024) The Cell Cycle Revisited: DNA Replication Past S Phase Preserves Genome Integrity. *Semin Cancer Biol*, 99:45- 55.
7. Saxena， S., and Zou, L. (2022) Hallmarks of DNA Replication Stress. *Mol Cell*, 82(12):2298- 2314.
8. Al Ahmad Nachar, B. and Rosselli, F. (2022) Safeguarding DNA Replication: A Golden Touch of MiDAS and Other Mechanisms. *Int J Mol Sci*,23(19):11331.
9. Bhowmick, R., Minocherhomji,S., Hickson, I.D.(2016) RAD52 Facilitates Mitotic DNA Synthesis Following Replication Stress. *Mol Cell*, 64(6):1117-1126.
10. Zhang, J., Dai, H., Huo, L., Burks, J.K., McGrail,D.J., Lin, S.Y. (2023) Cytosolic DNA Accumulation Promotes Breast Cancer Immunogenicity via a STING-Independent Pathway. *J Immunother Cancer*,11(10): e007560.
11. da Costa, A.A., Somuncu. O., Ravindranathan,R., Mukkavalli, S., Martignetti, D.B., *et al.* (2024) Single-Stranded DNA Gap Accumulation Is a Functional Biomarker for USP1 Inhibitor Sensitivity. *Cancer Res*, 84(20):3435-3446.
12. Chatzidoukaki O, Stratigi K, Goulielmaki E, Niotis G, Akalestou-Clocher A et al. (2021) R- Loops Trigger the Release of Cytoplasmic ssDNAs Leading to Chronic Inflammation upon DNA Damage. *Sci Adv*,7(47): eabj5769.
13. García-Muse， T. and Aguilera, A. (2019) R Loops: From Physiological to Pathological Roles. *Cell*,179(3):604-618.
14. Chen, Y.H., Keegan, S., Kahli, M. *et al.* (2019) Transcription Shapes DNA Replication Initiation and Termination in Human Cells. *Nat Struct Mol Biol* 26, 67–77.
15. Helmrich, A.; Ballarino, M.; Tora, L. (2011) Collisions between Replication and Transcription Complexes Cause Common Fragile Site Instability at the Longest *Human Genes. Mol. Cell,* 44, 966–977.

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