

**Research Article****A HYPOTHESIS THAT SHOULD HAVE WON A NOBEL PRIZE YEARS AGO: 3D GENOME STRUCTURE MIGHT BE CLOSELY LINKED TO THE MECHANISMS OF CANCER FORMATION AND CELL DIFFERENTIATION*****Gao-De Li**

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Abstract

Forty years ago, when I was 30-year-old, and through hard work, I published a Chinese-language hypothesis translated as “abnormalities in chromatin fiber configuration and malignant tumour formation” or “abnormal chromatin configuration and oncogenesis”. The hypothesis foreshadowed that study of 3D genome structure would eventually come and rightly predicted that 3D genome structure might be closely linked to the mechanisms of cancer formation and cell differentiation. Further, it posited that restoring the normal 3D genome structure of cancer cells could be the key to solving the cancer problem. In recent years, cancer reversion therapy has supported this prediction. Therefore, the hypothesis should have been a milestone in cancer and cell differentiation research, but eventually it became nothing because no articles worldwide have cited it. Taken together, I feel angry about article-citation prejudice in scientific community and believe that any relevant literature published in high-ranking or low-ranking journal should be cited. Also, I feel sad to weep the fate of my hypothesis and my unlucky life.

Keywords: Cancer, Cell differentiation, 3D genome structure, Chromatin fiber configuration, Fate of a hypothesis.

INTRODUCTION

The scientific community now recognizes that cancer cell formation, cell differentiation, and cancer reversal are all linked to 3D genome structure [1][2][3]. In 1986, I who was a teacher in the Second Military Medical University in Shanghai published a groundbreaking hypothesis named as “abnormalities in chromatin fiber configuration and malignant tumour formation” [4]. This was the world's first major hypothesis linking 3D genome structure to cancer cell formation and cell differentiation, which was a true “zero-to-one” breakthrough. We clearly remember that 40 years ago, cancer formation was widely recognised to be caused by gene mutations and no one thought that 3D genome structure could control the gene expression patterns. In this paper, I present the fate of my hypothesis, which foreshadowed the coming of 3D genome structure research and rightly predicted that 3D genome structure is closely associated with the mechanisms of cancer formation and cell differentiation.

THE FATE OF MY HYPOTHESIS

Several excerpts from my 1986-year original paper are illustrated here: “We collectively refer to the three-dimensional shape of chromatin fibers as ‘chromatin fiber configuration’; ‘chromatin fiber configuration is an objective reality, yet there are currently no technologies or instruments capable of visualizing the full configuration of chromatin fibers within the nuclei of living cells; we can only infer the configuration by observing the distribution of chromatin within the nucleus’; ‘It appears plausible that the differentiation process confers distinct gene activity patterns upon cells by establishing specific chromatin fiber configurations’; and ‘according to this hypothesis, there is no fundamental difference between malignant tumour cells and normal cells; while they exhibit many characteristics distinct from normal cells, these differences

do not stem from gene mutations but rather from abnormal chromatin fiber configurations within the nucleus and the associated aberrant gene activity. We believe that if the chromatin fiber configuration of tumour cells can be restored to the state characteristic of normal cells, all tumorigenic traits will vanish and normal cellular characteristics will re-emerge, thereby achieving the reversal of tumour cells.”

Research into 3D genome structure did not begin internationally until 2002 [5], sixteen years after I published this hypothesis. Subsequent years of research had confirmed the link between 3D genome structure and cancer formation and cell differentiation mechanisms. While it is perhaps understandable that international researchers, given that my article was written in Chinese, might not cite my work, the reluctance of domestic researchers to cite this significant hypothesis in the vast number of papers published on 3D genome structure warrants serious reflection. This hypothesis that has been validated by scientific experiments worldwide arguably deserved a Nobel Prize. Yet the domestic scientific community has neither cited nor supported it, allowing it to simply fade into oblivion. Was this great discovery destined to be buried? Or was my fate simply unlucky? Although the hypothesis that I published forty years ago when I was thirty-year old has recently been scientifically proven, it now appears to have no influence and remains virtually unknown. It should have been a milestone in cancer research, instead, it has failed to make even the slightest ripple in the vast ocean of the field.

Over a decade ago, I was overjoyed to discover quite by chance that my hypothesis had been scientifically validated. I hurriedly contacted the “Medicine and Philosophy” journal office, sending several emails, but received no response. Later, through Professor Guan Weibin of the Second Military Medical University, I obtained the email address of Academician Chen Yizhang from the same institution. I wrote to Academician Chen, explaining that my hypothesis had been proven and enclosing the relevant literature. Academician Chen replied promptly: “Li Gaode: I have received your letter and the

accompanying materials. Your decades of tireless dedication to scientific inquiry command great respect! However, due to the limitations of my own professional expertise, I find it difficult to offer an opinion on the content you provided. Please understand. I wish you success in your work and happiness in your life. Chen Yizhang."

I have realized then that there was no hope of gaining support or publicity for my discovery from my alma mater, the Second Military Medical University. Now retired, I could only pursue theoretical research and publish articles in low-cost, open-access journals to promote the hypothesis or theory that science had validated. In 2019, I published an English-language overview of the relationship between abnormal chromatin fiber configurations and cancer formation, formation of cell-type-associated chromatin configurations, and flexible cancer-associated chromatin configuration [6][7][8]. In 2020, I published work on the use of non-carcinogenic genotoxic drugs (NCGDs) to prevent and control all viral infections, proposing a novel antiviral theory [9][10]. In 2023, I published a hypothesis unifying the mechanisms of drug resistance across all cellular pathogens including cancer cells, bacteria, protozoa, and fungi [11]. In 2025, I published insights regarding the future direction of drug research [12], and in 2026, I published findings on the role of NCGDs in cancer prevention and treatment and revealing 3 medical principles [13][14]. All these papers relate to 3D genome structure. Current perspectives suggest that restoring the normal 3D genome structure of cancer cells is the key to solving the cancer problem (a view that rejects the notion that immunotherapy alone can resolve it). I recently proposed that NCGDs can alter the 3D genome structure of cancer cells [13], noting that appropriate NCGDs can transform cancer cells back into normal cells. Retinoic acid, belonging to NCGDs, serves as evidence of this, given its efficacy in treating acute promyelocytic leukaemia.

CONCLUSION

The fate of my hypothesis has been too poor to mention even though it foreshadowed that study of 3D genome structure would eventually come and correctly predicted that 3D genome structure might be closely associated with the mechanisms of cancer formation and cell differentiation at the time when gene mutations exclusively contributed to cancer formation. Further, the hypothesis posited that restoring the normal 3D genome structure of cancer cells could be the key to solving the cancer problem. In recent years, cancer reversion therapy has emerged to support this predicted decision [15]. Therefore, the appearance of this hypothesis should have been a milestone in cancer and cell differentiation research. But instead, it became nothing due to no citation worldwide. Altogether, I feel angry about article-citation prejudice in scientific community and believe that any relevant literature published in high-ranking or low-ranking journal should be cited. Also, I feel sad to weep the fate of my hypothesis and my unlucky life.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

REFERENCES

1. Jang, S., Yoo, K.H. (2026) 3D Chromatin Architecture in Cancer: Mechanisms of Dysregulation and Emerging Therapeutic Strategies. *Exp Mol Med* 58, 1734–1743.
2. Yost, K.E., Zhao, Y., Hung, K.L. *et al.* (2025) Three-Dimensional Genome Landscape of Primary Human Cancers. *Nat Genet* 57, 1189–1200.
3. Zheng, H., Xie, W. (2019) The Role of 3D Genome Organization in Development and Cell Differentiation. *Nat Rev Mol Cell Biol* 20, 535–550.
4. Li, G. D. Abnormalities in Chromatin Fiber Configuration and Malignant Tumour Formation [J]. *Medicine and Philosophy* (Humanities and Social Medicine Edition), 1986(2): 12-14.(in Chinese)
5. Dekker, J., Rippe, K., Dekker, M. and Kleckner, N. (2002) Capturing Chromosome Conformation. *Science*, 295, 1306-1311.
6. Li, G. D. (2019) Further Thoughts on Abnormal Chromatin Configuration and Oncogenesis. *Open Access Library Journal*, 6, e5185.
7. Li, G. D. (2019) Formation of Cell-Type-Associated Chromatin Configurations: A Hypothesis. *Open Access Library Journal*, 6: e5246.
8. Li, G.D. (2019) Flexible Cancer-Associated Chromatin Configuration (CACC) Might Be the Fundamental Reason Why Cancer Is So Difficult to Cure. *Open Access Library Journal*, 6, e5531
9. Li, G. D. (2020) Non-Carcinogenic Genotoxic Drugs Could Be Used to Prevent and Treat COVID-19. *Open Access Library Journal*, 7: e6536.
10. Li, G. D. (2026) Prevention of all viral infections by Non-Carcinogenic Genotoxic Drugs (NCGDS). *International Journal of Science Academic Research* Vol. 07, Issue 02, pp. 254-257.
11. Li, G. D. (2023) The Mechanism of Drug Resistance in Cellular Pathogens: A Hypothesis. *Open Access Library Journal*, 10: e10971.
12. Li, G. D. (2025) Orientation of Drug Development: Focusing on Gene Expression Alterations and Giving up the Mechanisms of Action of Drugs. *Open Access Library Journal*, 12: e13717.
13. Li, G. D. (2026) Non-Carcinogenic Genotoxic Drugs (NCGDS) and Cancer Prevention and Treatment. *International Journal of Science Academic Research* Vol. 07, Issue 03, pp. 560-563.
14. Li, G. D. (2026) Study of Non-Carcinogenic Genotoxic Drugs (NCGDs) might reveal Three Medical Principles. *International Journal of Science Academic Research*, 07, Issue 05, pp.808-810.
15. Oisakede EO, Olawade DB, Bello OJ, Analikwu CC, Egbon E, Fapohunda O, Boussios S. (2025) Cancer Reversion Therapy: Prospects, Progress and Future Directions. *Curr Issues Mol Biol*, 47(12):1049.
