Crimson Publishers
Wings to the Research

Short Communication

Genetic Processes in Eukaryotic Cells-A Cooperative Function Between Chromosomes and Extrachromosomal Circular DNA - and more?

Reinhard H Dennin*

Formerly: Academic Director, Head of Virology, Retd., Department of Infectious Diseases and Microbiology, University of Lübeck, UKSH, Campus Lübeck, Germany

***Corresponding author:** Reinhard H Dennin, Formerly: Academic Director, Head of Virology, Retd., Department of Infectious Diseases and Microbiology, University of Lübeck, UKSH, Campus Lübeck, Germany

Submission: July 19, 2021

Published: August 23, 2021

Volume 3 - Issue2

How to cite this article: Reinhard H Dennin*. Genetic Processes in Eukaryotic Cells-A Cooperative Function Between Chromosomes and Extrachromosomal Circular DNA - and more?. J Biotech Biores. 3(2). JBB. 000556. 2021.

Abstract

Apart from chromosomal DNA and mitochondrial DNA, eukaryotic cells contain Extrachromosomal Circular DNA (ECC-DNA). The ECC-DNA sequences are derived from chromosomal DNA. Their sizes range from some thousand bp up to mega bp. Their proportion of total cellular DNA can be up to 20%, both in cells from healthy people and people suffering from, e.g., tumors. Only recently have these ECC-DNAs gained attention in the context of diseases. A particular focus targets their involvement in oncology. The possible influence of ECC-DNA on chromosomal sequences in the Human Genome Project is addressed.

Keywords: Extrachromosomal Circular (ECC) DNA; Genetics; Diagnostic reservoir; Human genome

Introduction

This article describes interactions between chromosomal DNA and the ECC-DNAs. The findings indicate that particular genetic activities at the level of ECC-DNAs in the target cells with relevant potential for tumor development is in progress besides the chromosomes.

The Human Chromosomes

Chromosomes contain DNA with the genetic code for the blueprint of the respective organism. The Human Genome Projects (HGP) have already deciphered large parts of the DNA sequences of the human chromosomes. The "protein-coding genes represent less than 2% of the total genome sequence" [1], but careful considerations are necessary [2]. With the continuous improvements of the molecular protocols, the "number of errors when mapping …" could be reduced. [3] Apart from various sequences, e. g., belonging to Human Endogenous Retroviruses, the remaining sequences belong to the "non-coding regions" - not coding for proteins -, but contributing to regulatory factors, such as diverse forms of RNAs, transposons with various functionalities. The possible function of parts of the "non-coding regions" has gained further interest [4]. This situation may be important because of certain sequences are involved, e.g., as "enhancers", in development of cancer [5]. Even a genetic ablation of a specified RNA locus cause "genetic disorders" that can lead to organic malformations [6].

Extrachromosomal DNA

Besides the chromosomes, Extrachromosomal Circular DNA (ECC-DNA) in eukaryotic cells is a long-known fact [7]. The ECC-DNAs have a chromosomal origin, [8] mostly (?) containing coding and non-coding sequences. They "contribute to intercellular heterogeneity in normal and tumor cells" [9].

Genetic activities of ECC-DNAs

Obviously, there is an ongoing exchange of sequences between chromosomal (CHR) DNA and ECC-DNA. These ECC-DNAs may contain coding and non-coding sequences. Studies have

drawn attention because of the involvement of ECC-DNAs in the development of diseases, such as various aspects of tumors.

A. These findings apply in particular to the connection of ECC-DNAs in "oncogene amplification" [10], the generation of tumors, [11-14] their pathogenesis, resp. [15] and acceleration [16]. Certain details revealed on how ECC-DNAs "remodel" genomic DNA [17].

B. Implications in degenerative processes in the CNS [18].

C. Their features might provide basics for "biomarker developments" [19] and in applications already designed for diagnostic purposes [20,21]. Cell-free tumor DNA in plasma, circulating tumor DNA (ct-DNA) diagnostics should be standardized when tacking samples from the serum/plasma of presumed or already real, "personalized ct-DNA analysis" patients [22-23]. Is discrimination required to check the picked-up sequence's origin: CHR-DNA or ECC-DNA?

D. In Peripheral Blood Mononuclear Cells (PBMCs) of healthy individuals, ECC-DNAs were detectable; they contain sequences of the Non-Coding Region (NCR) of the Hepatitis C virus (HCV), showing individual methylation patterns (methylomes) [24].

Possible impact of ECC-DNA on the human genome project (HGP)?

The HGP is designed to reveal the sequences of the DNA of human chromosomes, as a basis for gene identification. Apart from constitutive considerations about a human reference genome, [25] a possible interacting factor on the chromosomal sequences is not mentioned: the ECC-DNAs? The point is that only the sequestration of the ECC-DNA from chromosomal DNA may warrant pure/genuine chromosomal DNA sequences, i.e., not distorted by ECC-DNAs. Have the sequencing alignments been checked at scientific standards to exclude sequences of ECC-DNAs?

Protocol to search for ECC-DNA

The "ECC splorer" protocol [26] may be a tool for this task in the aftermath. A database for ECC-DNAs is available [27].

The human reference genome

In consideration of various details, there are requests for a new human "reference genome" [28]. The facts of the interactions between CHR-DNA and ECC-DNAs, should promote basic studies to exclude sequences of ECC-DNAs.

Final comment

The ECC-DNAs in eukaryotic cells are facts; however, what is inducing their generation: individual genetic rearrangements due to endogenous triggers or upon exogenous elicitors, or both? So far, the ongoing research has drawn attention on the ECC-DNAs, mainly because of their involvement in cancer development and possible use in diagnostics. ECC-DNAs with as yet unknown other coding potential should be considered in healthy individuals. The human genome project: It requires clarification on how was explicitly excluded on scientific standards the possible influence of ECC-DNAs on the chromosomal DNA sequences; this means, among other things, possible confounding factors have to be excluded beforehand.

References

1. Sana J, Faltejskova P, Svoboda M, Slaby O (2012) Novel classes of non-coding RNAs and cancer. J Transl Med 10: 103.
2. Clamp M, Fry B, Kamal M, Xie X, Cuff J, et al. (2007) Distinguishing protein-coding and noncoding genes in the human genome. PNAS 104(49): 19428-19433.
3. Knutsen A (2020) A new human reference genome represents the most common sequences. The Scientist.
4. Vitsios D, Dhindsa RS, Middleton L, Gussow AB, Petrovski S, et al. (2021) Prioritizing non-coding regions based on human genomic constraint and sequence context with deep learning. Nat Commun 12(1): 1504.
5. Cao K, Shilatifard A (2019) An introduction: Enhancers in cancer: Genetic and epigenetic deregulation. Encyclopedia of Cancer (Third Edition).
6. Allou L, Balzano S, Magg A, Quinodoz M, Royer-Bertrand B, et al. (2021) Non-coding deletions identify Maenli lncRNA as a limb-specific En1 regulator. Nature 592(7852): 93-98.
7. Møller HD, Mohiyuddin M, Prada-Luengo I, Sailani RM, Halling JF, et al. (2018) Circular DNA elements of chromosomal origin are common in healthy human somatic tissue. Nat Commun 9: 1069.
8. Cohen S, Agmon N, Sobol O, Segal D (2010) Extrachromosomal circles of satellite repeats and 5S ribosomal DNA in human cells. Mob DNA 1(1): 11.
9. Kumar P, Kiran S, Saha S, Paulsen T, Chatrath A, et al. (2020) ATAC-seq identifies thousands of extrachromosomal circular DNA in cancer and cell lines. Science Advances 6(20): eaba2489.
10. Verhaak RG, Bafna V, Mischel PS (2019) Extrachromosomal oncogene amplification in tumour pathogenesis and evolution. Nat Rev Cancer 19(5): 283-288.
11. Wang M, Chen X, Yu F, Ding H, Zhang Y, et al. (2021) Extrachromosomal circular DNAs: Origin, formation and emerging function in Cancer. Int J Biol Sci 17(4): 1010-1025.
12. Liao Z, Jiang W, Ye L, Li T, Yu X, et al. (2020) Classification of extrachromosomal circular DNA with a focus on the role of extrachromosomal DNA (ecDNA) in tumor heterogeneity and progression. Biochim Biophys Acta Rev Cancer 1874(1): 188392.
13. Wang T, Zhang H, Zhou Y, Shi J, et al. (2021) Extrachromosomal circular DNA: A new potential role in cancer progression. J Transl Med 19(1): 257.
14. Li R-Y, Liang Z-Y (2020) Circulating tumor DNA in lung cancer: real-time monitoring of disease evolution and treatment response. Chin Med J (Engl) 133(20): 2476-2485.
15. Yan Y, Guo G, Huang J, Gao M, Zhu Q, et al. (2020) Current understanding of extra-chromosomal circular DNA in cancer pathogenesis and therapeutic resistance. J Hematol Oncol 13(1): 124.
16. Bailey C, Shoura MJ, Mischel PS, Swanton C (2020) Extrachromosomal DNA-relieving heredity constraints, accelerating tumour evolution. Annals of Oncology 31(7): 884-893.
17. Koche RP, Rodriguez-Fos E, Helmsauer K, Burkert M (2020) Extrachromosomal circular DNA drives oncogenic genome remodeling in neuroblastoma. Nature Genetics 52(1): 29-34.
18. Ain Q, Schmeer Ch, Wengerodt D, Witte OW, Kretz1 A (2020) Extrachromosomal circular DNA: Current knowledge and implications for CNS aging and neurodegeneration. Int J Mol Sci 21(7): 2477.
19. Sin STK, Jiang P, Deng J, Ji L, Cheng SK, et al. (2020) Identification and characterization of extrachromosomal circular DNA in maternal plasma. Proc Natl Acad Sci USA 117(3): 1658-1665.

20. Zhu J, Chen S, Zhang F, Wang L (2018) Cell-free eccDNAs: A new type of nucleic acid component for liquid biopsy? Mol Diagn Ther 22(5): 515-522.

21. Keller L, Belloum Y, Wikman H, Pantel K, et al. (2021) Clinical relevance of blood-based ctDNA analysis: Mutation detection and beyond. Br J Cancer 124(2): 345-358.

22. Bratman SV, Yang SYC, Iafolla MAJ, Liu Z, Hansen AR, et al. (2020) Personalized circulating tumor DNA analysis as a predictive biomarker in solid tumor patients treated with pembrolizumab. Nat Cancer 1: 873-881.

23. Said R, Guibert N, Oxnard GR, Tsimberidou AM (2020) Circulating tumor DNA analysis in the era of precision oncology. Oncotarget 11(2): 188-211.

24. Dennin RH, Wo JE (2019) DNA sequences homologous to hepatitis C virus (HCV) in the extrachromosomal circular DNA in peripheral blood mononuclear cells of HCV-negative subjects. J Zhejiang Univ Sci B 20(8):637-646.

25. Miga KH (2021) Breaking through the unknowns of the human reference genome. Nature 590(7845): 217-218.

26. Mann L, Seibt KM, Weber B, Heitkam T (2021) ECCsplorer: A pipeline to detect extrachromosomal circular DNA (ECCDNA) from next-generation sequencing data. bioRxiv.

27. ECC-DNAdb (2020) The extrachromosomal circular DNA database. Homo sapiens.

28. Ballouz S, Dobin A, Gillis JA (2019) Is it time to change the reference genome? Genome Biol 20(1): 159.