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ADAPTIVE EVOLUTION OF TRANSCRIPTION REGULATION AGAINST SOLAR UV RADIATION CAUSES CODON BIAS IN HUMAN PROTEIN CODING GENES

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ABSTRACT

***Objective**: Solar ultraviolet (UV) radiation is both cytotoxic and mutagenic to humans. It is linked with both melanoma and nonmelanoma skin cancers. Cyclobutane pyrimidine dimers are the predominant DNA lesion induced by the UV radiation. Thymine dimer makes three quarters of the total pyrimidine dimers. Transcription and DNA replication are severely hampered by these DNA lesions if they are left unrepaired. In this present study, we analysed whether human genes avoid the UV-sensitive UU codons. **Methods:** The frequency of UV-sensitive thymine dinucleotides were computed using data analysis in molecular and evolution (DAMBE) software tool. Relative synonymous codon usage was also computed using DAMBE software tool. Microarray transcription profiles of human WS1 skin fibroblast cells irradiated with UV radiation was downloaded from NCBI database. **Results**: UU codons are preferred in a set of human protein coding genes and at the same time avoided in another set of genes. **Conclusion**: We found that the adaptation to mediate efficient DNA damage response through transcription causes the bias in the usage of UU codons. This strategic usage of synonymous codon helps cells to mediate efficient DNA damage response upon UV irradiation.*

KEY WORDS

Adaptation, synonymous codons, DNA damage response, transcription regulation

INTRODUCTION

Solar ultraviolet radiation (UVR) reaching the terrestrial ecosystem contains UVA and UVB, whereas the high energy UVC is observed by the ozone layer. Exposure to UV radiation can damage the DNA in skin cells directly or by producing reactive oxygen species. Structural distortions in DNA induced by UVR will interrupt transcription and DNA replication. Several DNA repair pathways efficiently recognizes these DNA lesions and fixes them before they interfere with transcription and replication. If the damage is irreversible cells activates apoptosis pathways to avoid the risk of mutations and tumor cell formation. The most common DNA lesion induced by UVR is cyclobutane pyrimidine dimer (CPD) between two pyrimidine bases. Among other dipyrimidines, thymine-thymine dipyrimidines (TT) are the most vulnerable target for UVR. Around three quarters of total CPDs induced by UVR consists of thymine-thymine dimers (T<>T). T<>T has very slow repair rate when compared to other CPDs [1-14]. Moreover, T<>Ts are produced within a picosecond upon exposure to UVR [15]. DNA damage from solar UVR exposure is linked with increased risk of basal cell carcinoma, squamous cell carcinoma and melanoma. The nonmelanoma skin cancer is the most prevalent cancer in white skin populations particularly northern Europeans, being a huge burden for healthcare sector. Keeping this in mind, in the present study we analysed whether the complete coding sequences (CDS) of human genes avoids the most UV sensitive dinucleotide TT by using synonymous codons, thereby minimizing the risk of predisposition to T<>T formation. We found that synonymous UU codons were found to be preferred in a group of genes which are downregulated

upon UV irradiation and avoided in another group of genes which are upregulated upon UV irradiation. The intrinsic regulation of gene expression by T<>T upon UV irradiation causes the bias in the usage of UU codons.

MATERIALS AND METHODS

Sequence data

Protein coding genes of human nuclear genome were retrieved using gene type filters of Ensembl BioMart. The full list of genes with their sequence identity number, name, chromosomal location and gene size are provided in supplemental file 1. Complete coding sequences (CDS) for the protein coding genes were retrieved using gene filters and attribute filters of Ensembl BioMart.

Data analysis

Data analysis in molecular biology and evolution software DAMBE was used to compute the dinucleotide frequency of thymine dinucleotides. Relative synonymous codon usage (RSCU) was also computed using DAMBE software tool.

Transcription profiles of UV irradiated cells

I retrieved top 500 genes individually from upregulated and downregulated genes from microarray profiles of WS1 human skin fibroblasts exposed to UVC-254nm at 50J/m^2-high-dose [16]. Genes were assigned as upregulated or downregulated by comparing raw transcription profiles of cells from 6h control and 6h post irradiation. The average value of two replicates were used for both 6h control and 6h post irradiation.

RESULTS & DISCUSSION

It was recognised that anti-apoptotic genes are larger in size than pro-apoptotic genes. And it has been suggested that upon DNA damage the loss of expression of either anti-apoptotic genes or pro-apoptotic genes will decide cell fate, whether to undertake repair or to undergo apoptosis [17]. So, it seems that anti-apoptotic genes are hardwired to be large or larger genes are assigned for anti-apoptosis, which will predispose them to more damage since the UV-induced DNA damage is random in genome, and this will make the damage surveillance a more strategic one. Further, this will mediate appropriate gene expression regulation required at the moment.

Similarly, TT will intrinsically regulate gene expression by transcriptional arrest upon UV irradiation through T<>T formation. Since T<>Ts are highly abundant and get repaired slowly, we hypothesized that gene transcription upon UV irradiation will be determined by the number of TT found in a gene or by the number of UU codons found in a coding sequence (CDS).

So, first we tested our hypothesis by using transcription profiles of UV irradiated cells. Complete coding sequences (CDS) were retrieved for top 500 upregulated genes. Using DAMBE software tool relative synonymous codon usage (RSCU) of UU codons were computed. Likewise, CDS were retrieved and RSCU were computed for top 500 downregulated genes. Four amino acids having both UU codons and synonymous non-UU codons were chosen for the analysis. They are Val (GUU, GUC, GUA, GUG), Phe (UUU, UUC), Leu (UUA, UUG, CUU, CUC, CUA, CUG) and Ile (AUU, AUC, AUA). The data in figure 1 shows that our hypothesis is true that the downregulated genes are rich in TT frequency and prefers synonymous UU codons and vice versa in the upregulated genes. The exemption Leu has six synonymous codons, of which the UU codons CUU and UUA directly correlates with geneic TT frequency, and the exemption UUG has been reported as equally effective alternative start codon for translation initiation in eukaryotes, interestingly, under conditions of amino acid starvation UUG initiation has shown higher translation rate than AUG [18], suggests that the more usage of UUG in low TT frequency genes may increase the translation rate under stress, since many metabolic processes including amino acid metabolism will be slowed down by UV radiation.

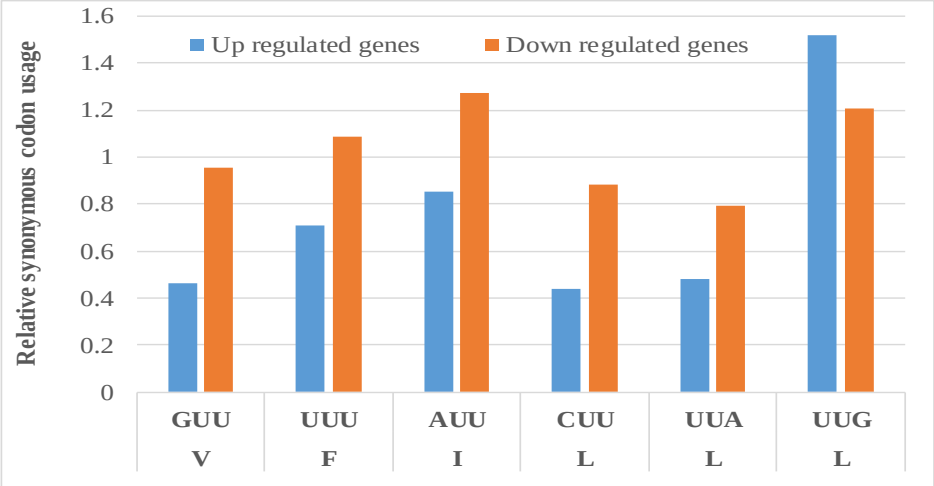

Figure 1. Association between codon usage and transcription: Codon usage was compared between the upregulated genes and the downregulated genes upon UV irradiation. The amino acids Val, Phe, Ile and Leu have synonymous UU codons and non-UU codons. Upregulated genes avoid UU codons, thereby decreases the risk of thymine dimer formation in the DNA and are being transcriptionally efficient.

Next, we computed the frequency of TT in all 19042 protein coding genes of human nuclear genome. Then we analysed the correlation between geneic TT frequency and relative synonymous codon usage of UU codons. Four amino acids having both UU codons and synonymous non-UU codons were chosen for the analysis. They are Val (GUU, GUC, GUA, GUG), Phe (UUU, UUC), Leu (UUA, UUG, CUU, CUC, CUA, CUG) and Ile (AUU, AUC, AUA). Complete coding sequences (CDS) were retrieved for top 1000 genes with higher TT frequency. Using DAMBE software tool relative synonymous codon usage (RSCU) of UU codons were computed. Likewise, CDS were retrieved and RSCU were computed for top 1000 lowest TT frequency genes. The data shows that the usage of synonymous UU codons directly correlates with geneic TT frequency (Fig. 2).

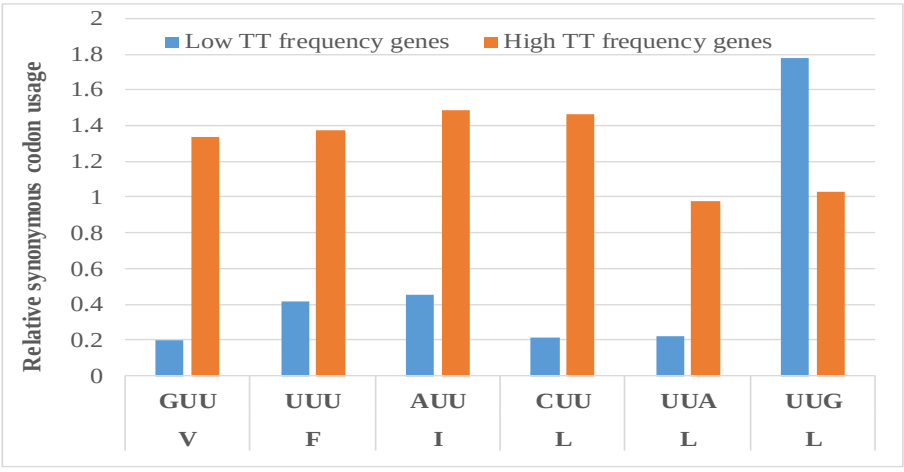

Figure 2. Association between codon usage and TT dinucleotide frequency of genes: Codon usage was compared between genes with high TT dinucleotide frequency and genes with low TT dinucleotide frequency. The TT dinucleotide frequency of genes directly correlates with the usage of UU codons.

CONCLUSION

Taken together, it is clear that synonymous UU codons are preferred in a group of genes which are downregulated upon UV irradiation and avoided in another group of genes which are upregulated upon UV irradiation. Our findings suggest that the intrinsic regulation of gene expression through transcriptional arrest by T<>T upon UV irradiation causes the bias in the usage of UU codons, which in the other hand helps human cells to mediate efficient DNA damage response required at the moment.

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REFERENCES

[1] Vink, A. A. & Roza, L. Biological consequences of cyclobutane pyrimidine dimers. Journal of photochemistry and photobiology. B, Biology 65, 101-104 (2001).

[2] Brash, D. E. *et al.* A role for sunlight in skin cancer: UV-induced p53 mutations in squamous cell carcinoma. Proceedings of the National Academy of Sciences of the United States of America 88, 10124-10128 (1991).

[3] Ziegler, A. *et al.* Mutation hotspots due to sunlight in the p53 gene of nonmelanoma skin cancers. Proceedings of the National Academy of Sciences of the United States of America 90, 4216-4220 (1993).

[4] Chadwick, C. A. *et al.* The detection of cyclobutane thymine dimers, (6-4) photolesions and the Dewar photoisomers in sections of UV-irradiated human skin using specific antibodies, and the demonstration of depth penetration effects. Journal of photochemistry and photobiology. B, Biology 28, 163-170 (1995).

[5] Young, A. R. *et al.* Human melanocytes and keratinocytes exposed to UVB or UVA in vivo show comparable levels of thymine dimers. The Journal of investigative dermatology 111, 936-940, doi:10.1046/j.1523-1747.1998. 00435.x (1998).

[6] Applegate, L. A., Scaletta, C., Panizzon, R., Niggli, H. & Frenk, E. In vivo induction of pyrimidine dimers in human skin by UVA radiation: initiation of cell damage and/or intercellular communication? International journal of molecular medicine 3, 467-472 (1999).

[7] Bykov, V. J., Jansen, C. T. & Hemminki, K. High levels of dipyrimidine dimers are induced in human skin by solar-simulating UV radiation. Cancer epidemiology, biomarkers & prevention: a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 7, 199-202 (1998).

[8] Bykov, V. J., Sheehan, J. M., Hemminki, K. & Young, A. R. In situ repair of cyclobutane pyrimidine dimers and 6-4 photoproducts in human skin exposed to solar simulating radiation. The Journal of investigative dermatology 112, 326-331, doi:10.1046/j.1523-1747.1999. 00523.x (1999).

[9] Cadet, J., Sage, E. & Douki, T. Ultraviolet radiation-mediated damage to cellular DNA. Mutation research 571, 3-17, doi: 10.1016/j.mrfmmm.2004.09.012 (2005).

[10] Douki, T., Reynaud-Angelin, A., Cadet, J. & Sage, E. Bipyrimidine photoproducts rather than oxidative lesions are the main type of DNA damage involved in the genotoxic effect of solar UVA radiation. Biochemistry 42, 9221-9226, doi:10.1021/bi034593c (2003).

[11] Mouret, S. *et al.* Cyclobutane pyrimidine dimers are predominant DNA lesions in whole human skin exposed to UVA radiation. Proceedings of the National Academy of Sciences of the United States of America 103, 13765-13770, doi:10.1073/pnas.0604213103 (2006).

[12] Rochette, P. J. *et al.* UVA-induced cyclobutane pyrimidine dimers form predominantly at thymine-thymine dipyrimidines and correlate with the mutation spectrum in rodent cells. Nucleic acids research 31, 2786-2794 (2003).

[13] Xu, G., Snellman, E., Bykov, V. J., Jansen, C. T. & Hemminki, K. Effect of age on the formation and repair of UV photoproducts in human skin in situ. Mutation research 459, 195-202 (2000).

[14] Young, A. R. *et al.* The in-situ repair kinetics of epidermal thymine dimers and 6-4 photoproducts in human skin types I and II. The Journal of investigative dermatology 106, 1307-1313 (1996).

[15] Schreier, W. J. *et al.* Thymine dimerization in DNA is an ultrafast photoreaction. Science 315, 625-629, doi:10.1126/science.1135428 (2007).

[16] Gentile, M., Latonen, L. & Laiho, M. Cell cycle arrest and apoptosis provoked by UV radiation-induced DNA damage are transcriptionally highly divergent responses. Nucleic acids research 31, 4779-4790 (2003).

[17] Ljungman, M. & Lane, D. P. Transcription - guarding the genome by sensing DNA damage. Nature reviews. Cancer 4, 727-737, doi:10.1038/nrc1435 (2004).

[18] Ingolia, N. T., Ghaemmaghami, S., Newman, J. R. & Weissman, J. S. Genome-wide analysis in vivo of translation with nucleotide resolution using ribosome profiling. Science 324, 218-223, doi:10.1126/science.1168978 (2009).

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