

Does 5G FR2 cause genomic instability in human skin? An *in vitro* study in primary skin cells

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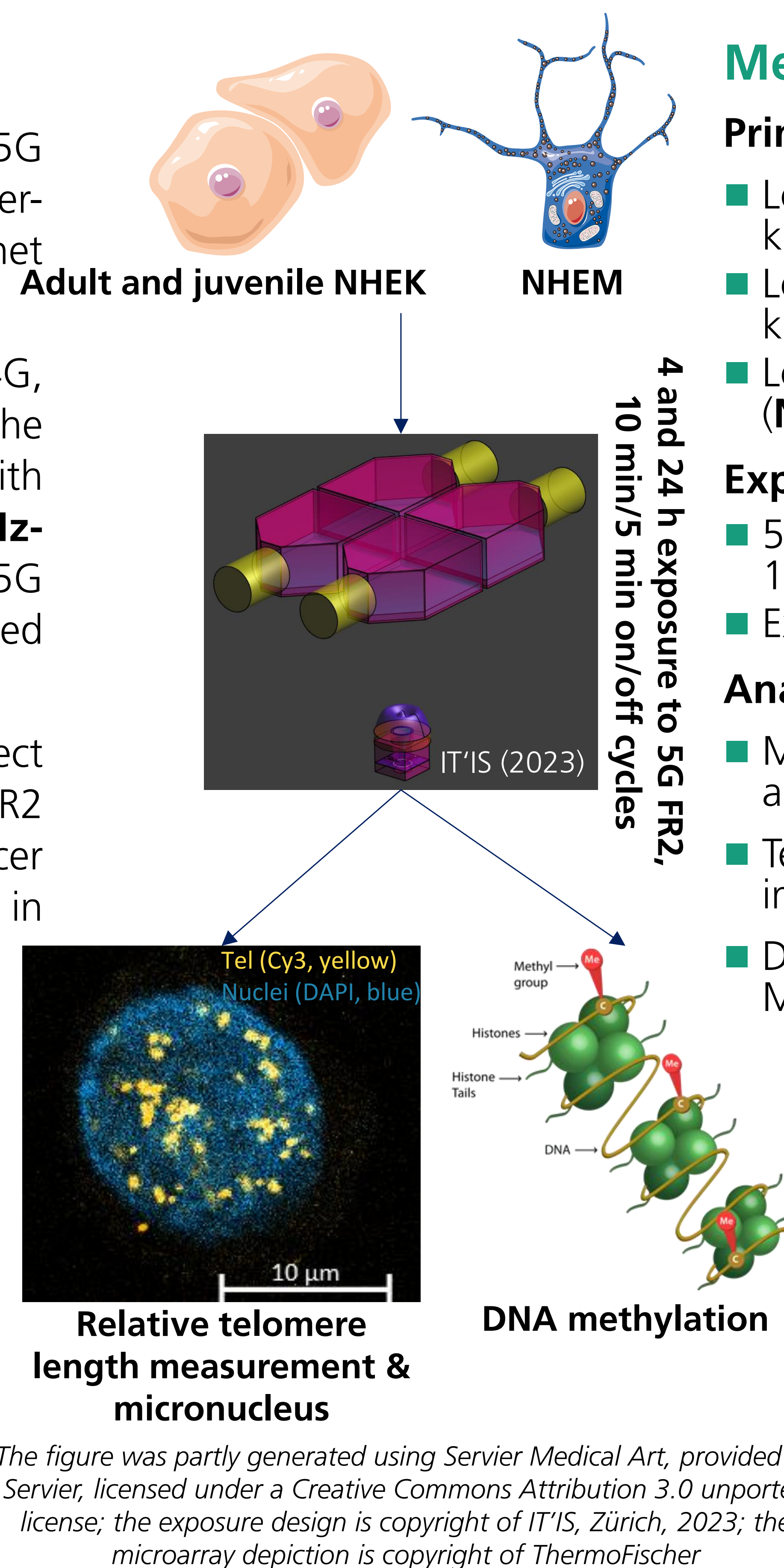
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Introduction

The fifth generation of mobile phone technology (5G New Radio) was rolled out in 2020 to meet the ever-increasing demand for stable and fast internet connection.

A major change to 5G NR in comparison to 1G to 4G, which uses the frequency range 1 (FR1; <6 GHz) is the utilization of the frequency range 2 (FR2) with millimeter wavelength (mmWave; 24.25 GHz-52.6 GHz). Currently, data on potential adversity of 5G FR2 are limited, whereas FR1 has been studied extensively in the last 30 years.

The European Union Horizon Europe-funded project SEAWave aimed to investigate effects of 5G FR2 exposure on human health, focused on skin cancer induction, as 5G FR2 has low penetration depth in human tissue.



Methods

Primary human skin cell model:

- Low-pigmented male juvenile epidermal keratinocytes (**NHEK-f.c.**)
- Low-pigmented female adult epidermal keratinocytes (**NHEK-c.**)
- Low-pigmented female adult epidermal melanocytes (**NHEM**)

Exposure:

- 5G FR2 power density: 3.33 W/m² (**low**), and 10 W/m² (**high**), sham exposure as negative control
- Exposure duration: 4 h & 24 h

Analysis:

- Micronucleus assay with detection of aneugenicity and clastogenicity using PNA FISH
- Telomere length measurement using PNA FISH and image analyzer
- DNA methylation using Illumina Infinium MethylationEPIC v2 array (935K)

Micronucleus

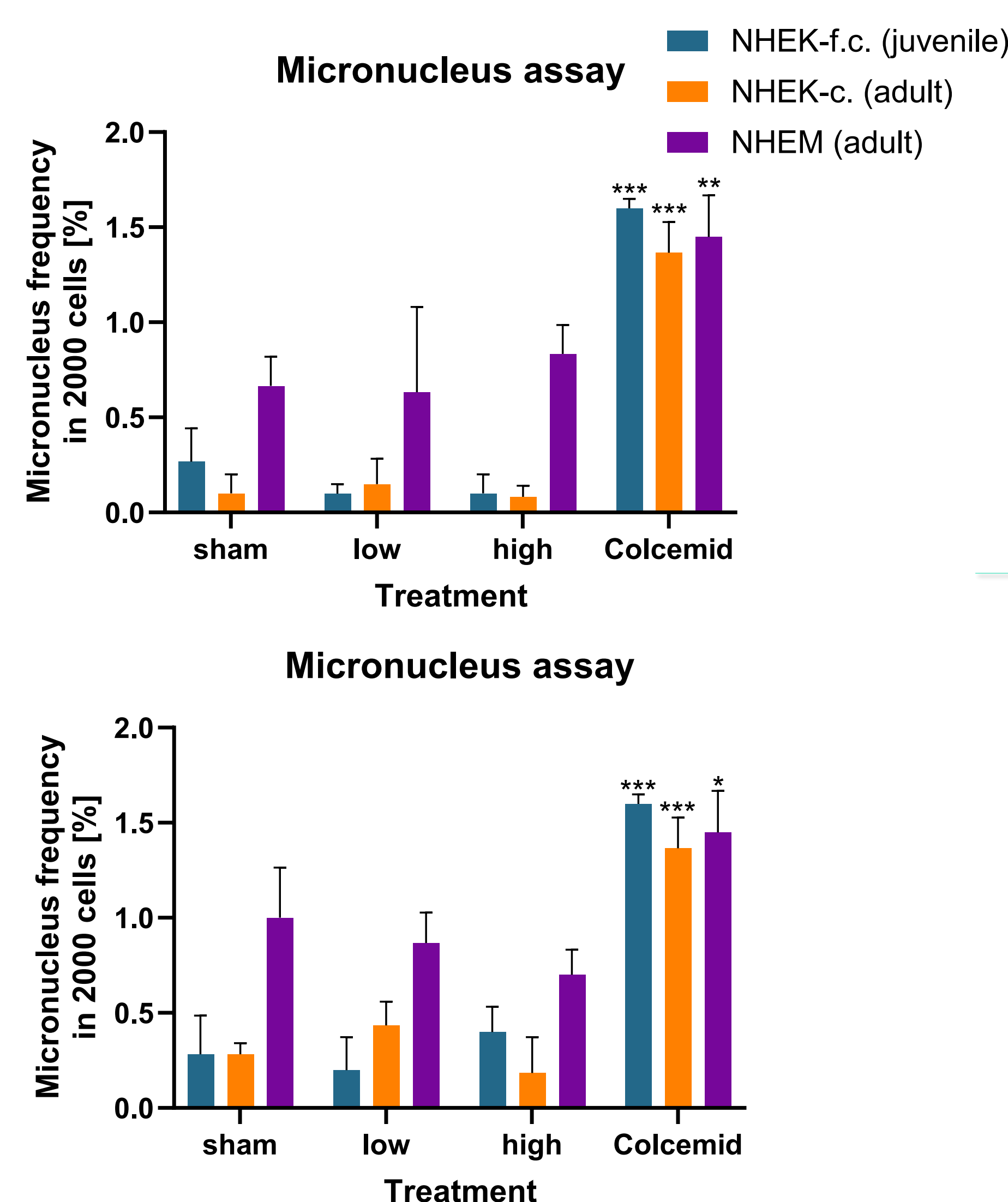


Figure 1: Micronucleus assay following 5G FR2 exposure on NHEK-f.c. (blue), NHEK-c. (orange) and NHEM (purple). Cells were pre-cultured for 24 (NHEK) or 72 h (NHEM) and then exposed to 5G FR2 for 4 (top) or 24 h (bottom). Data are derived from the micronucleus frequency of 2000 nuclei (in %) and represent means \pm SD of three independent experiments. Statistics was performed using One-Way ANOVA with Dunnett's multiple comparison test, compared to respective sham-exposed sample. Statistical comparison between Colcemid positive controls with the respective negative controls was done using one-tailed Student's *t*-test, where * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

DNA methylation

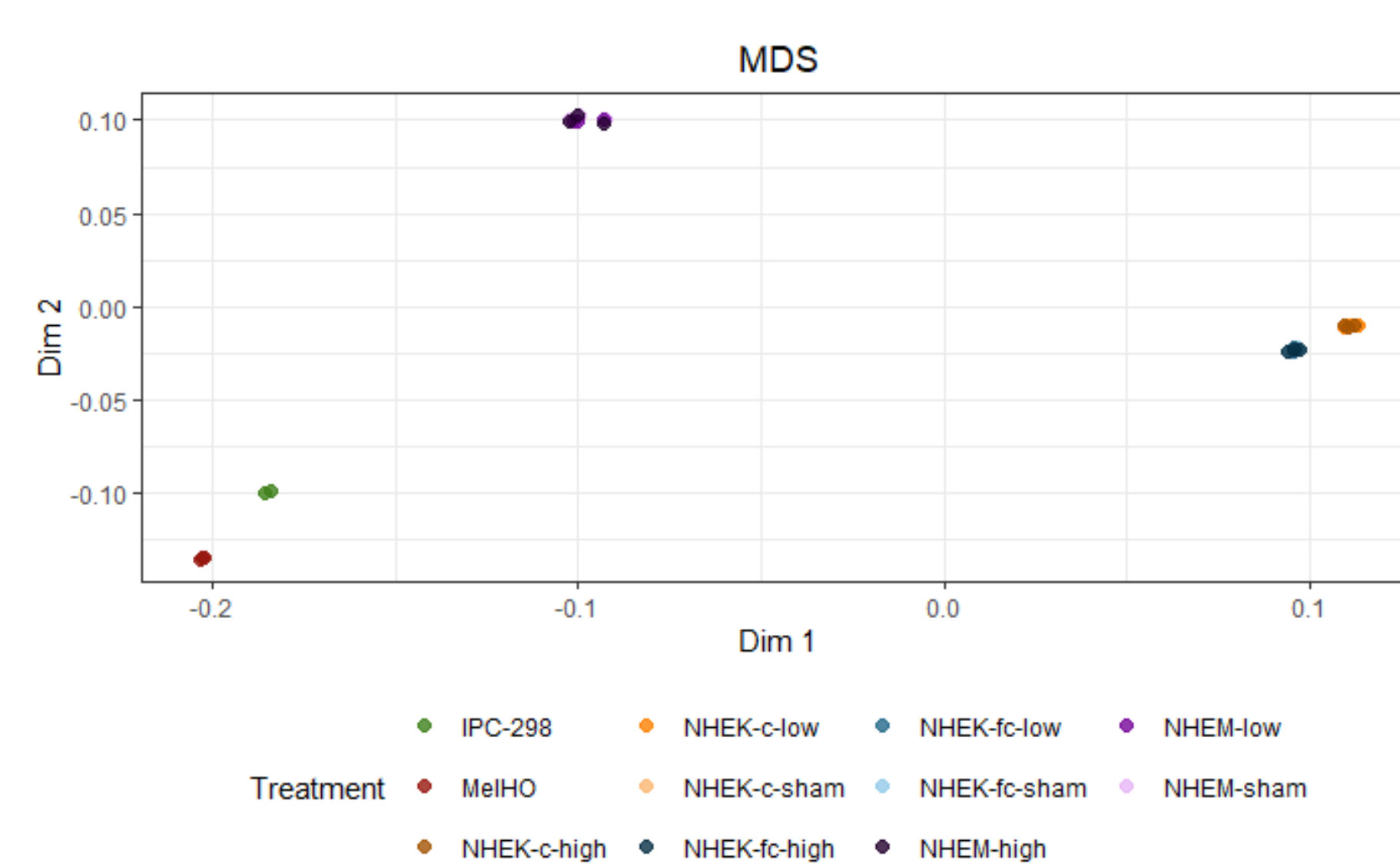


Figure 2: Genome-wide DNA methylation analysis following 5G FR2 exposure on NHEK-f.c. (blue), NHEK-c. (orange) and NHEM (purple) as well as melanoma reference cell lines MelHO (red) and IPC-298 (green). Cells were pre-cultured for 24 (NHEK) or 72 h (NHEM) and then exposed to 5G FR2 for 24 h. Multidimensional scaling shows mapping of DNA methylation datasets obtained from each treatment group using R software with SeSaMe, DMRcate and Gviz packages.

Telomere length measurement

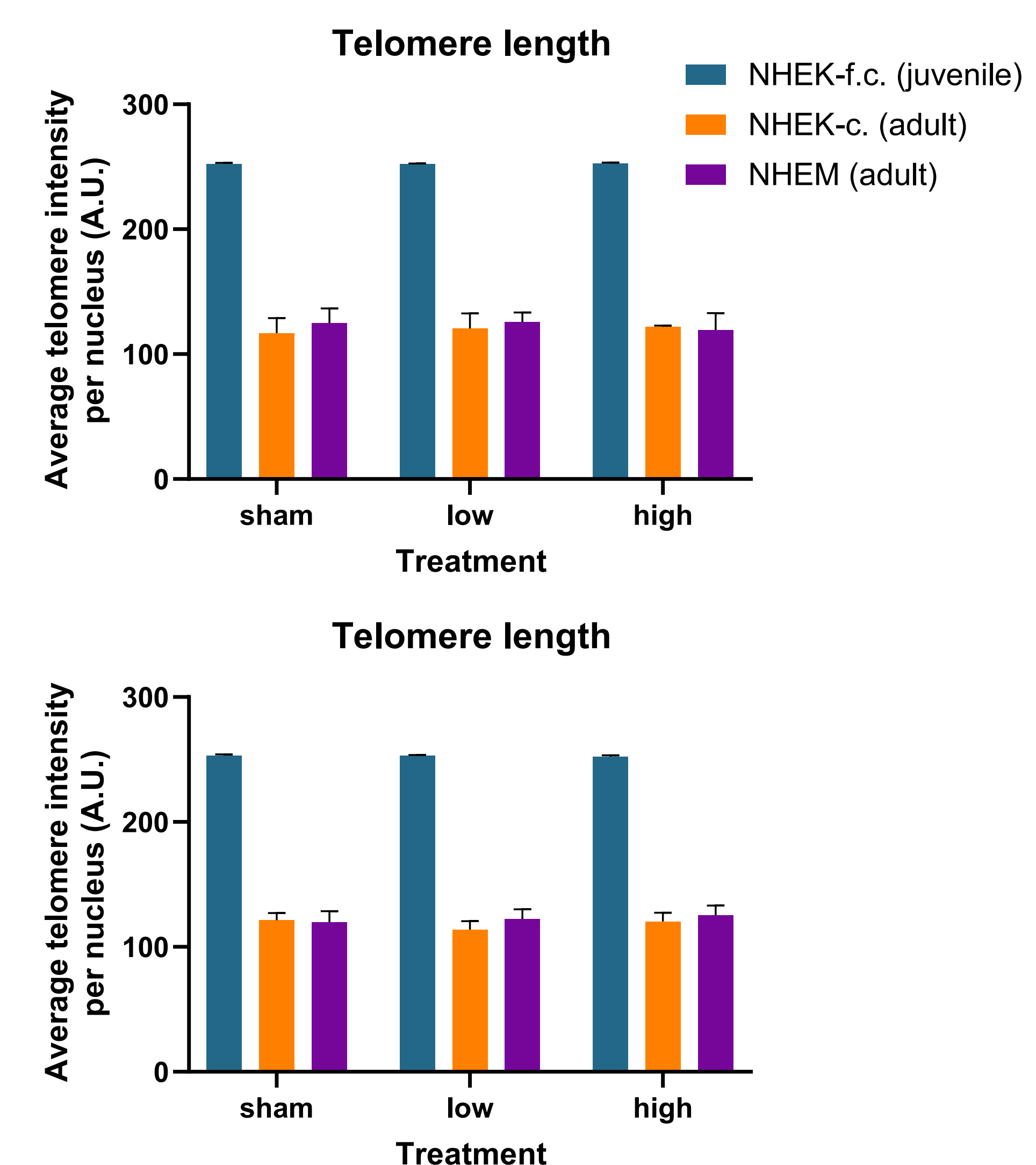


Figure 3: Telomere length measurement following 5G FR2 exposure on NHEK-f.c. (blue), NHEK-c. (orange) and NHEM (purple). Cells were pre-cultured for 24 h (NHEK) or 72 h (NHEM) and then exposed to 5G FR2 for 4 h (top) or 24 h (bottom). Average telomere intensity per nucleus was quantified from digitized fluorescent signals using semi-automated software. Data represent mean \pm SD of three independent experiments ($n \geq 40$ nuclei per round).

Summary & Conclusions

- 4 h and 24 h of exposure to 5G FR2 is shown to not induce any micronucleus formation and changes in telomere intensity or length.
- DNA methylation landscape remained unchanged after 24 h of exposure to 5G FR2
- Based on previous observations and the present study, 5G FR2 exposure seems not induce genomic instability.
- Future analyses will investigate 5G FR2-dependent changes in the microRNA landscape.

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This project has received funding from the Horizon Europe Research and Innovation programme under Grant Agreement No 101057622