Experimental and human population studies of DNA lesions in healthy individuals

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DNA damage is a valuable biomarker in human molecular epidemiology being associated with many diseases. However, the level of DNA damage is influenced also by intrinsic features of healthy persons: heredity, sex, age and body type. The objective of this review was to summarize data on DNA breakage level in healthy humans depending on their characteristics and to compare these data with experimental studies and observations on animals dealing with the same factors. Several strains of laboratory animals manifest an increased level of DNA breaks. In humans some gene polymorphisms are associated with [an] increased level of DNA damage, however it is believed that environmental factors are more important. In animals a higher level of DNA breakage is usually detected in males. In humans data on the role of gender are contradictory and depend on race. Experimental models provide evidence of increased levels of single- and double-strand breaks in obese animals. Human studies are not so convincing, an increase of double-strand breaks appears to be a more reproducible feature of DNA of overweight persons. Data on single-strand DNA breaks in aged persons are contradictory, but double strand breaks evidently increase with age.

K e y w o r d s: DNA breaks, aging, gender, obesity

Introduction

DNA damage by irradiation, chemicals and endogenous free radicals and further ineffective repair of these lesions are common cases of premature aging, cancer [1, 2], diabetes mellitus [3], neuropathies [4] and other diseases [5]. Treatment strategies of cancer and diabetes mellitus can be aimed at the DNA damage prevention and DNA repair enhancement [6, 7]. On the other hand DNA breaks and other lesions are involved in physiological processes like cell differentiation [8, 9]. Simplicity and precision of the "comet assay" or single cell electrophoresis have expanded substantially the circle of studied cases. DNA breaks are evaluated in

healthy people unexposed to DNA-damaging factors depending on their gender, age, place of residence, bad or good habits, *etc*. Here we will try to summarize the data of some of such trials, focusing on intrinsic features of healthy persons: heredity, sex, age and body type comparing them with the data of experimental studies aimed at similar questions.

Genome

Existence of mice strains containing higher levels of DNA breaks is a well-established fact. A good example of such strains is the mice strain 101/H characterized by high incidence of tumours, short life span, decreased DNA repair efficiency and deafness. The molecular weight of single-strand DNA fragments from the 101/H mice foetal fibroblasts was found to be lower than that in CBA mice [10]. Unfortunately the gene responsible for above traits of 101/H strain is not revealed yet. Similarly, non-irradiated lymphoblasts of radiosensitive strain (LY-S cells) showed higher average DNA-mobility and heterogeneity in DNA-comet length as compared to the cells of radioresistant strain (LY-R). This difference is suggested to be compatible with a relatively higher background DNA-breakage in LY-S cells due to deficiency in repair of double-strand breaks in these cells [11]. Nowadays several mice strains with the characterized mutations and high level of spontaneous DNA breaks are characterized. For example, the senescence-accelerated mouse prone 8 (SAMP8) develops the accelerated senescence phenotype largely mediated by oxidative stress, due to the mutation in the *Ogg*1 gene, greatly reducing an ability of the enzyme to excise 8-hydroxy,2'-deoxyguanosine (8OHdG)

adducts. Males of this strain have a high level of DNA damage in caudal epididymal spermatozoa as measured by the alkaline Comet assay [12]. DNA strand breaks are increased in Fanconi anaemia mouse model strain Fancd2(-/-), but not in Fancg(-/-) mice [13]. A persistent level of the intrinsic DNA damage in fibroblasts derived from the MRL mouse was revealed by both neutral and alkaline comet assay. These mice are characterized by an increased capacity for regeneration and down-regulation of p21 protein of p53/p21 axis [14]. When the mice of three different strains were deprived of sleep, statistically significant differences in DNA damage were found in blood cells of the Swiss mice strain when compared to negative controls [15].

The data of studies in human population indicate some dependence of the DNA breakage level on genetical background. For example, the DNA breakage level in white blood cells is lower in black Americans compared to their white compatriots [16]. [The] Dependence of spontaneous level of DNA breaks in Czech population was reported for [the] XPC Ala499Val (C→T) single nucleotide polymorphism [17], however these data were not reproduced in other trial performed in the same population, it turned out that Asp1104His in the *XPG* gene is more important, carriers of 1104His have a higher level of DNA breaks [18]. Despite the above data, a comparison of DNA repair capacity in twins indicates greater importance of environmental factors compared to hereditary factors [19].

Gender

Data of some experiments indicate the dependence of the level of DNA lesions on gender.

For example, stress induces DNA breaks in hippocampus of rat males, but not females [20], the same dependence was observed in rat cubs separated from their mothers [21]. In dab (*Limanda limanda*) males, fishes living in natural conditions, DNA was also stronger damaged compared to females [22]. Males of wood mice (*Apodemus sylvaticus*) are much more susceptible to pollution compared to females, however no difference in DNA breakage was observed in animals living in non-polluted areas [23].

The population study performed in Sweden indicated a higher level of single-strand breaks in men, compared to women [24]. Two studies performed in Czech Republic gave opposite results [17, 18]. In black Americans, women had a higher level of DNA breaks, in white Americans the level of DNA breakage was the same in men and women [25]. Great contradictions between the studies do not allow making any conclusion about humans.

Body mass and obesity

The results of several studies in animals indicate an increase of DNA breaks in obese animals. This fact was confirmed on Zucker rats, the caloric restriction decreased the level of both single-strand [26] and double-strand breaks [27]. The difference was well-pronounced in sperm cells of Zucker rats [28] and two murine models of obesity [29] and parrots kept in captivity [30]. In fat mice, the pattern of promoter methylation and spectrum of microRNAs resemble these parameters in irradiated mice [31]. However, the level of oxidative DNA damage in Zucker rats was the same in several tissues of lean and obese animals, the former had even higher level of oxidised bases in hepatocytes [32]. Some facts indicate that *obesity* could be consequence, but not the cause of DNA damage, knockout of the oxoguanineglycosylase 1 gene, encoding an enzyme removing the oxidised base, caused obesity in mice [33].

The data of population studies are much more contradictory. More DNA breaks were detected in overweight young Swedish women compared to lean girls, however this difference was not observed in men [24] and in male Chinese cooks [33]. In adipocytes obtained during surgery on lean and obese persons the level of DNA breaks was the same [35]. Dependence of the level of DNA breaks on the body weight was not observed in Austrians, but the level of 8-oxoguanidine was even higher in lean persons [36]. A lower 8-oxoguanidine level was detected in blood plasma of obese Turks [37] and in urine of Croatians with recently diagnosed metabolic syndrome [38]. However, some studies indicate increased levels of the oxidised base and DNA breaks in obese and metabolic syndrome patients [37, 39, 40]. Loss of weight does not increase the DNA repair capacity, this was shown on a group of elderly Canadian women, who decreased their weight by 10 % [41]. The changes in DNA repair capacity were very modest also in a group of Spanish men, who put down their weight [42]. Studies on the DNA double strand breaks give more significant results, compared to studies of other DNA lesions. In white blood cells of obese adolescents the level of the DNA double-strand breaks was 6 times higher, compared to lean children [43]. Some studies indicate increased level of the DNA double-strand breaks also in spermatocytes of overweight men [44], however this result is not always reproduced [45].

Age

Numerous experimental studies indicate an increase of the level of DNA damage with age. The normal variations in basal DNA damage were detected by Comet assay in leukocytes from 45 female and male mice from different age groups (newborns, 3.5, 12, and 104 weeks); significantly increased values in 104 week old mice, as compared to other ages were revealed [46]. DNA damage in white blood cells of Swiss mice, measured as a tail moment in the single-cell gel electrophoresis in peripheral blood of different age groups of mice (1, 6, 12 and 18 months) showed a gradual increase with age more pronounced in females [47]. A significant DNA damage was revealed in the cardiomyocytes of rapidly aging SAMP8 mice when compared with SAMR1 mice with normal life span [48]. The level of DNA damage in brain cells from SAMR1 was unchanged from 4 to 15 months of age. In the case of SAMP1 brain cells, the DNA breaks increased in an age-related manner from 8 to 15 months of age. In the cases of liver and kidney, no changes were observed in both strains from 4 to 15 months of age. [49]. DNA damage in bone marrow cells from young and aged apoE-/- mice compared with age-matched wild-type C57BL/6 (C57) mice, that was measured using the comet assay was higher in young apoE-/- mice than in age-matched C57 mice, and increased in aged C57 and apoE-/- mice [50]. DNA breaks are increased also in the hematopoietic stem cells derived from old mice [51]. When the comet assay was used to investigate the level of oxidatively damaged DNA in several organs of ApoE(-/-) mice as strand breaks, endonuclease III- and formamidopyrimidine DNA glycosylase-sensitive sites, the level of DNA damage mainly increased with age in the liver, whereas no increase was observed in the aorta or lung of the mice [52]. The 8-oxodGuo levels were also significantly higher in older mouse liver DNA. The primary lung fibroblasts cultured from older mice had significantly greater levels of strand breaks than cells derived from young mice [53]. The level of oxidized purines and pyrimidines was found to be higher in aortic cells of 26 months old mice compared to six months old mice [54].

The data on wild rodents are not so convincing. The effects of environmental pollution on genetic damage in wood mice (*Apodemus sylvaticus*) were investigated by means of the comet assay at several sites in Belgium differing in the level of pollution, with special attention to the role of age as a potential confounding variable. A significant increase in genetic damage with age was observed at the most polluted sites, but not at the clean sites [23].

Some authors report an increase of DNA damage in lymphocytes in old rats [55], others observe an opposite trend [56]. In whole blood nucleated cells the level of DNA breaks increased in 19 months old rats compared to 2 months old rats [57], in 9 months old rats the difference was not yet detectable [58]. The breaks could be observed in optic nerve of old rats [59], the DNA single- and double-strand breaks as well as the oxidative damage increased also in astrocytes and neurons [60]. Similar increase was observed in livers and kidneys of old rats [61], but in these organs alkali-labile sites were the only age-related DNA lesions, no increase in double-strand breaks was observed [62] (Hashimoto *et al.*, 2007). Thus, the experimental studies indicate an increase of DNA lesions with aging, how-

ever some contradictory data have been published. To overcome these contradictions, a combined parameter, "differential of DNA lesions" has been proposed [63]. The study was conducted on mice leukocytes, the authors did not detect any increase in the level of single-strand breaks, however the level of oxidised purines increased in animals of both sexes, oxidised pyrimidines – in males only, double-strand breaks - in females. Calculation of the "differential of DNA lesions", taking into account the level of oxidized purines, double strand breaks and DNA methylation levels, indicated an obvious increase of DNA lesions with age. Nowadays the double-strand breaks are considered by many scientists as the most important in aging [64]; it is supposed that these DNA lesions form a link between an increase of entropy with age and process of senescence [65]. It was hypothesized that the strongest argument in favour of determinative role of double-strand breaks in senescence could be the increased life span of animals with strong expression of the proteins involved in repair of double-strand breaks. The promising results were obtained on mice with [the] hyperexpressed SIRT 6 transcription factor [66]. Inefficient repair of double-strand breaks and decreased expression of the enzymes involved in non-homologous end joining were observed also in the fibroblasts derived from elderly persons. The transfections of plasmids with XRCC4 and DNA ligase 4 genes, causing hyperexpression of these proteins, triggered rejuvenation of these cells [67]. Comparison of the expression of enzymes involved in repair of double-strand breaks in short living (mouse) and long-living (humans and the nude mole rat) species indi-

cates a higher efficiency of above repair process in long-living species [68]. A controlled induction of double-strand breaks by transfection of adenovirus with Sac I restrictase gene triggered the signs of senescence in the liver of mice [69]. The DNA breaks caused by photosensitizing compounds [70] and heat shock lead to comparable effects [71].

Compared to the experimental data, the results of human population studies are far from being convincing. After reviewing numerous publications on the topic it was concluded that no definite assertion is possible, some publications indicate an increase, whereas others – decrease or stable level of DNA lesions with aging [72]. Some authors admit the accumulation of double-strand breaks, but not oxidative lesions or single-strand breaks [73]. Using a novel modification of immunofluorescence method, an increase of γH2AX foci (marker of double-strand breaks) in lymphocytes with age was demonstrated, but the conclusion was true only for persons of Hispanic origin [74]. In a scrupulous study performed by Løhr and co-authors [75], no increase of single strand breaks was revealed, the oxidised bases increased only in elderly women. The latter parameter correlated with the cholesterol level and other metabolic deviations. Thus, the classical question: "Which came first, the chicken or the egg?" emerges. It is well known that the cholesterol level increases with age and is involved in the development of the senile phenotype.

Conclusions

The experimental studies provide an apparent evidence of dependence of the level of DNA breaks on the intrinsic features of organisms like genotype, gender, age and body type. The

results of population studies confirm the same trends, but are not so convincing. To our opinion, an application of other methods, pulse-field gel electrophoresis for example, in combination with "monopolising" comet assay could enhance the credibility and reproducibility of the results. Increasing number of studies performed not only on white blood cells, but also on buccal epithelium or other accessible human tissues could lead to clearer conclusions.

Funding

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Експериментальні та популяційні дослідження рівня пошкоджень ДНК е здорових організмах

Н. Сьяксте

Пошкодження ДНК є інформативним біомаркером для молекулярної епідеміології, так як вони пов'язані з багатьма захворюваннями людини. У той же час рівень пошкоджень ДНК може залежати від внутрішніх властивостей притаманних здоровим людям: спадковості, статі, віку і статури. Метою даного огляду є узагальнення даних щодо розривів ДНК у здорових людей в залежності від їхніх характеристик у порівняння з даними експериментів і спостережень за тваринами. У лабораторних тварин кількох ліній спостерігають підвищений рівень розривів ДНК, у людини - кілька генних поліморфізмів асоційовані з підвищеним рівнем розривів, але вважається, що визначальними є зовнішні фактори. У самців тварин ДНК пошкоджена сильніше, ніж у самиць, дані по людині суперечливі і залежать від раси. Експериментальні моделі показують підвищений рівень одно- і дволанцюгових розривів ДНК при ожирінні. Дані досліджень на людині менш переконливі, краще відтворюються дані щодо підвищеного рівеня дволанцюгових розривів ДНК у людей із зайвою вагою. По одноланцюгових розривах ДНК при старінні дані суперечливі, переконливо показано зростання дволанцюгових розривів ДНК з віком.

К л ю ч о в і   с л о в а : розриви ДНК, старіння, стать, ожиріння.

Экспериментальные и популяционные исследования уровня повреждений ДНК в здоровых организмах

Н. Сьяксте

Повреждения ДНК являются информативным биомаркером для молекулярной эпидемиологии, так как они связаны со многими заболеваниями человека. В то же время уровень повреждений ДНК может зависеть от внутренних свойств, присущих здоровым людям, от наследственности, пола, возраста и телосложения. **Целью** данного обзора будет обобщение данных о разрывах ДНК у здоровых людей в зависимости от их характеристик и сравнение с данными экспериментов и наблюдений на животных. У лабораторныз животных нескольких линий наблюдают повышенный уровень разрывов ДНК, у людей несколько генных полиморфизмов ассоциированы с повышенным уровнем разрывов, но считается, что определяющими являются внешние факторы. У самцов животных ДНК повреждена сильнее, чем у самок, данные по людям противоречивы и зависят от расы. Экспериментальные модели указывают на повышенный уровень одно- и двунитевых разрывов ДНК при ожирении. Данные исследований на людях менее убедительны, лучше воспроизволдятся данные, указывающие на повышенный уровень двунитевых разрывов ДНК у людей с лишним весом. Данные по однонитевым разрывам ДНК при старении противоречивы, убедительно показано нарастание двунитевых разрывов ДНК с возрастом.

К л ю ч е в ы е   с л о в а : разрывы ДНК, старение, пол, ожирение.