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CLONAL HAEMATOPOIESIS AND IONIZING RADIATION: RISKS FOR HEMATOLOGICAL MALIGNANCIES AND SOMATIC DISEASES

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Introduction. The influence of radiation-induced genetic instability on the formation of clonal expansion is a relevant problem in health monitoring and preventive diagnostics of oncohematological and somatic pathology in individuals exposed to long-term low-dose anthropogenic irradiation, such as nuclear industry workers and radiation diagnostics doctors.

Objective. Identification of possible application points of preventive diagnostics of genome instability markers and clonal hematopoiesis in groups of individuals exposed to long-term low-dose anthropogenic irradiation.

Results and discussion. Genetic instability in genes of epigenetic regulation (*DNMT3A*, *TET2*, *ASXL1*), signaling pathways and cell proliferation (*JAK2*, *FLT3*), DNA repair regulators (*TP53*, *PPM1D*), RNA splicing factors (*SF3B1*, *SRSF2*) most often initiates clonal hematopoiesis, which is realized more frequently by myeloid and less frequently by lymphoid neoplasia. The influence of clonal hematopoiesis on the development of somatic diseases is mediated by the combined effect of carrying these mutations and the processes of chronic inflammation. Low-dose ionizing radiation is capable of initiating clonal expansion mainly due to mutations in *DNMT3A* and *TET2* genes. There is a lack of studies on the assessment of increased morbidity against the background of clonal hematopoiesis in groups of occupational risk of low-dose ionizing radiation exposure (workers in the nuclear industry and doctors of radiation diagnostics), which requires further study.

Conclusions. Studies aimed at identifying risk markers of morbidity growth in the setting of clonal hematopoiesis in groups of workers exposed to long-term anthropogenic action of low-dose ionizing radiation form the basis for developing cohort-oriented programs of disease prevention in these individuals.

Keywords: genetic instability; clonal hematopoiesis; clonal hematopoiesis of undetermined potential; low-dose ionizing radiation; somatic mutation

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КЛОНАЛЬНОЕ КРОВЕТВОРЕНИЕ И ИОНИЗИРУЮЩЕЕ ИЗЛУЧЕНИЕ: РИСКИ РАЗВИТИЯ ОНКОГЕМАТОЛОГИЧЕСКОЙ И СОМАТИЧЕСКОЙ ПАТОЛОГИИ

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Введение. Влияние радиационно-индуцированной генетической нестабильности на формирование клональной экспансии актуально для мониторинга здоровья и превентивной диагностики онкогематологической и соматической патологии у лиц, подвергающихся длительному воздействию техногенного облучения в малых дозах (работники атомной промышленности и врачи лучевой диагностики).

Цель. Выявление возможных точек приложения превентивной диагностики маркеров нестабильности генома и клонального кроветворения у групп лиц, подвергающихся длительному воздействию техногенного облучения в малых дозах.

Обсуждение. Генетическая нестабильность в генах эпигенетической регуляции (*DNMT3A*, *TET2*, *ASXL1*), сигнальных путей и клеточной пролиферации (*JAK2*, *FLT3*), регуляторов репарации ДНК (*TP53*, *PPM1D*), факторов сплайсинга РНК (*SF3B1*, *SRSF2*) наиболее часто инициирует клональное кроветворение, реализующееся чаще миелоидными и реже лимфоидными неоплазиями. Влияние клонального кроветворения на развитие соматических заболеваний опосредовано сочетанным действием носительства указанных мутаций и процессами хронического воспаления. Ионизирующее излучение в малых дозах способно инициировать клональную экспансию преимущественно за счет мутаций в генах *DNMT3A* и *TET2*. Исследований по оценке повышения заболеваемости на фоне развития клонального кроветворения в группах профессионального риска воздействия малых доз ионизирующего излучения (работники атомной промышленности и врачи лучевой диагностики) в настоящее время мало, что требует дальнейшего изучения.

Выводы. Исследования по выявлению маркеров риска роста заболеваемости на фоне развития клонального кроветворения в группах работников, подвергающихся длительному техногенному действию ионизирующего излучения в малых дозах, позволят сформировать когортно-ориентированную программу профилактики заболеваний у данных лиц.

Ключевые слова: генетическая нестабильность; клональное кроветворение; клональное кроветворение неустановленного потенциала; малые дозы ионизирующего излучения; соматическая мутация

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INTRODUCTION

Research into the radiation-induced genetic instability and its interrelation with clonal expansion is a relevant direction with regard to health monitoring of nuclear industry workers and radiologists. Identification of risk factors in the emergence of adverse consequences in these categories of individuals, along with dispensary monitoring and timely prophylaxis, may contribute to combating the development of related pathologies [1].

On a daily basis, human beings are exposed to low-dose ionizing radiation (IR) emitted both by natural (environmental radionuclides found in the atmosphere, soil, and water) and artificial or man-made sources. The cumulative effect of all types of natural radiation is defined as the natural radioactive background. The global average values of such radiation in different regions of the world range from 2.4 to 4.0 mSv/year, with the average level in the Russian Federation comprising 3.36 (from 2.10 to 8.60) mSv/year [1–3].

The impact of IR on humans is realized through the influence of the natural radioactive background, occupational exposure at the workplace, as well as when receiving medical care (medical exposure). The widespread use of IR in medical and other industries, primarily in the nuclear power industry, contributes to an increase in radiation exposure of workers. Thus, for a certain list of industries, where additional anthropogenic exposure to IR is possible, the limit of permissible effective IR dose reaches 5 mSv/year for Group B personnel and 20 mSv/year for Group A personnel [3].

At present, the immediate and delayed consequences of human exposure to high-dose IR in technogenic catastrophes, characterized by critical changes leading to defects in the functioning of organs and systems, have been studied and described in sufficient detail. At the same time, exposure to low-dose IR, although without clinical manifestations of radiation damage, may also induce damage at the genetic and epigenetic levels, with the effect depending on the radiation dose in a non-monotonic polymodal character. The recent data points to the effect of low-dose radiation on genome instability, modifying cellular and tissue processes. This may eventually contribute to changes in the body sensitivity to the action of additional non-radiation factors [4–6].

Over the past decade, research interest has been revolving around clonal hematopoiesis (CH), considering it as a biological condition predisposing to the development of malignant blood disorders (MBD), solitary tumors, cardiovascular pathology, autoimmune diseases, and other pathologies [7–9].

This work aims to identify the possibility of preventive diagnostics of genome instability markers and CH markers in work groups exposed to long-term low-dose technogenic irradiation.

RESULTS AND DISCUSSION

General understanding about clonal hematopoiesis

Hematopoietic cells of the bone marrow (BM) exhibit the highest proliferative potential. The processes of blood cell

proliferation and differentiation in BM are carried out continuously. About one trillion blood cells are formed daily. The basis of hematopoiesis are hematopoietic stem cells (HSCs), which have the ability to differentiate into all mature cells of peripheral blood. It was first postulated by Prof. A.A. Maximov in 1909. The hematopoiesis model proposed by Maximov was confirmed by experimental data obtained in the era of active study of radiation effects on the human body [10].

Over the past decades, our understanding of the hematopoiesis system has been significantly extended [10–13]. Thus, numerous studies have advanced the idea of continuous differentiation landscapes having a few or no discrete differentiation stages and smooth cell state transitions. In this context, cells in a heterogeneous pool of progenitors differentiate along multiple potential trajectories that contain some branching points determining the fate of a particular cell. However, the notion that the progeny of a single HSC represents a clone of a particular HSC remains unchanged. The normal hematopoietic system is polyclonal that assumes production of “own” cell clones by different HSCs and maintenance of their number as well as the ratio of cells with varied degrees and directions of differentiation in BM within stable limits. Hematopoietic cells with a high proliferative activity are characterized by accumulation of genetic “breaks” with increasing number of divisions [14].

Upon human aging, physiological quantitative and qualitative changes occur in hematopoiesis, including a decrease in the total proliferative HSC activity with a relative increase in their total number, an increase in the erythroid precursors number, a decrease in the lymphoid precursors number with age-related changes in the immune system function. In general, hematopoiesis tends to oligoclonality [15]. Genetic and epigenetic processes most likely underlie the age-related changes in BM. The age-related decrease of HSC regenerative potential [16], specific changes in expression of transcription regulator genes, accumulation of somatic mutations [17], and pronounced shortening of telomeric chromosome parts [18] were noted. In addition, in elderly people, increased expression of genes involved in the regulation of apoptosis and inflammation in the hematopoiesis system was detected; however, in young people, the activity of genes regulating the processes of proliferation and metabolic activity of hematopoietic progenitor cells is high. All the described trends are manifestations of regular processes characterizing changes in hematopoiesis in the process of aging of the organism [19].

At the same time, the accumulation of mutations can lead to a CH with activated proliferation of one HSC or more differentiated hematopoietic progenitor cell and with formation of a progeny clone carrying gene mutations. While CH is not an independent nosology, it can be an intermediate stage between normal hematopoiesis and MBD [20]. It has been shown that CH can arise as a result of neutral drift or directed selection. In the case of neutral drift, all cell clones initially have equal chances of their contribution to the formation of the pool of self-renewing HSCs; the decisive influence is exerted by random processes, such as depletion of the stem cell pool. In the case of directed selection, somatic changes influence the selective growth advantage in

certain HSC clones relative to others, with the subsequent clonal expansion [21].

In 2014, two independent groups published the results of large-size studies conducted using next-generation sequencing (NGS). According to the data obtained, CH is associated with somatic mutations most frequently occurring in three genes of epigenetic regulation of transcription. These include *DNMT3A* — a gene encoding a protein that performs de novo methylation; *TET2* — encoding a protein that catalyzes the conversion of the modified DNA base methylcytosine into 5-hydroxymethylcytosine and participates in the transcription process regulation; and *ASXL1* — encoding a nuclear protein involved in the epigenetic regulation of gene expression and in the process of chromatin remodeling. The obtained results were confirmed in a study of groups of patients with different types of MBD and solid neoplasms [22, 23]. The work by M. Xie et al. convincingly demonstrated that mutations in *DNMT3A*, *TET2*, *ASXL1*, and *TP53* genes occurred most frequently and almost in all analyzed nosological subgroups [24].

In 2015, on the basis of the accumulated data, the term “clonal hematopoiesis of indeterminate potential” (CHIP) was coined. Thus, CHIP is defined in the presence of a hematopoietic cell clone with a gene mutation associated with the risk of MBD in the absence of cytopenia and criteria of other hematological diseases, according to the classification of the World Health Organization. The allele load level of the indicated gene should be not less than 2% (the value is accepted as the minimum clinically significant threshold level for the next-generation sequencing method — NGS), and for X-linked genes in men — not less than 4% [25, 26]. The frequency of mutation detection increases with age, and their presence is associated with an increased risk of MBD. It was determined that about 15–20% of people over 70 years of age without oncohematological diseases have somatic mutations associated with an increased risk of oncopathology [27]. Later, the term “age-related clonal haematopoiesis” was proposed for such changes, which is defined in elderly patients with a somatic mutation in genes regardless of its clinical significance and allele load level, as well as with no changes in the hemogram and MBD criteria [23, 27].

The term “clonal haematopoiesis of oncogenic potential” (CHOP) was introduced to designate the state of carrying mutations that can act as a direct driver of MBD [28, 29]. The allocation of such a category and the approach to the division of genes according to their direct role in the development of MBD (i.e., their oncogenic potential) is currently rather tentative and debatable, thus requiring data accumulation and analysis.

The term “clonal cytopenia of undetermined significance” can also be found in the scientific literature, which is characterized by the presence of somatic mutations in the gene(s) associated with MBD, with an allele burden of at least 2% (or 4% in men in the case of X-linked genes mutations); absence of criteria for MBD, other causes of cytopenia and molecular aberrations; persistent cytopenia in more than one hematopoietic growth (hemoglobin less than 100 g/L, neutrophils less than 1.8×10^9 /L, platelets less than 100×10^9 /L) for at least four months. The term “idiopathic cytopenia of undetermined significance”

(idiopathic cytopenia of undetermined significance) is also proposed to be used in the presence of persistent cytopenia in more than one hematopoietic growth and in the absence of criteria for myeloid neoplasm and other blood system diseases [30].

Clonal hematopoiesis and oncohematological diseases

It has been proven that individuals with CH are more likely to show signs of genetic instability due to somatic mutations in epigenetic regulation genes (*DNMT3A*, *TET2*, *ASXL1*), RNA splicing genes (*SF3B1*, *SRSF2*, *ZRSR2*), signaling pathways and cell proliferation (*JAK2*, *FLT3*), genes related to metabolism and cell differentiation (*IDH1*, *IDH2*), and in DNA repair regulation genes (*TP53*, *PPM1D*). In comparison with the overall population, such individuals are also frequently diagnosed with cytopenia of unclear etiology. Mutations in *DNMT3A*, *TET2*, and *ASXL1* genes account for about 80% of CHIP cases [22, 23].

Mutations characteristic of myelodysplastic syndrome (MDS), myeloproliferative neoplasms, and acute myeloid leukemia are observed in *JAK2*, *PPM1D*, *TP53*, *SRSF2*, and *SF3B1* genes, being less frequent [26]. The frequency of detection of these mutations is much higher than the incidence of MBD; nevertheless, CH can be considered as an event preceding the development of hemoblastosis. Signs of CH are revealed in 50% of patients with aplastic anemia; CH-specific *DNMT3A* and *ASXL1* gene mutations are found in 15% of patients [31, 32]. Another example of CH with its transformation into a pathological process is paroxysmal nocturnal hemoglobinuria. In this disease, the clone arisen from HSCs with glycosyl-phosphatidylinositol deficiency is less susceptible to T-cell-mediated destruction in comparison with normal HSCs [30, 33].

In addition, CH with point mutations or structural variations, such as gene copy number changes, leads to a ten-fold increase in the risk of MBD. The role of antitumor immunity disorders in the transformation of CH into MBD requires further investigation [22]. At the same time, the presence of CHIP is associated with a 13-fold increase in the risk of hemoblastosis, with the frequency of its occurrence in 0.5–1% of patients per year [8].

In most cases, CHIP is benign, especially when the clone size is small and multiple, without driver mutations [20]. The main risk factors for the development of the disease (not only hematologic but also somatic) into CHIP include: a significant clone size (10% or more) and its growth acceleration, clonal changes in more than one cell line, multiple driver mutations, *TP53* gene mutations, and chromosomal aberrations [34].

Until recently, the accumulated information and expansion of detectable genetic mutations spectrum has not allowed differentiation of mutations that initiate the onset of CH from those that are an early event in the development of MBD, as well as to identification of second-order mutations that make the most significant contribution during the disease progression. Thus, the isolation of driver mutations, passenger mutations, and background and cooperating mutations has been proposed [20, 22]. The works published in 2024 indicate that methods have already been

developed to identify driver mutations, such as “a method for enriching nonsynonymous mutations over neutral synonymous mutations” or machine learning based algorithms [35, 36].

Thus, in accordance with modern concepts, mutations of genes associated with CHIP is a predisposing factor in MBD. Appearance of such mutations leads to transformation of normal HSC into “pre-leukemia” neoplastic HSC. Altered HSC gives rise to small subclones and, itself, does not practically differ from normal HSC. The frequency of mutation detection increases with age, being a natural biological process accompanying aging. However, “pre-leukemia” HSC has an increased risk for transformation into leukemia HSC at acquisition of additional molecular-genetic damages. Factors in such transformations require further study. Classification of genetic breakages according to their oncogenic potential is also an area of interest for current research. The CH model presented in Fig. 1 summarizes our ideas about driver, cooperating, passenger, and background mutations, as well as the causes of genetic instability that determine clonal evolution with the development of MBD.

Clonal hematopoiesis and somatic pathology

The development of CHIP is an independent risk factor concerning not only various hemoblastoses, but also cardiovascular diseases, Alzheimer’s disease, type 2 diabetes mellitus, thrombosis, autoimmune processes, and other pathologies [7]. The clonal expansion of HSC encounters no anatomical restrictions, with clone cells circulating in the bloodstream in large numbers [21]. Thus, CH is associated with an increased risk of developing both MBD (more often myeloid and less often lymphoid) and various somatic pathologies [21, 37].

A number of publications have convincingly demonstrated that CHIP correlates with the risk of acute leukemia, MDS, and other hemoblastoses, as well as with such adverse cardiovascular events, as acute cerebral circulatory disorder and acute myocardial infarction [38–40]. Two independent meta-analysis studies also showed the link of CHIP with a high risk of atherosclerosis and cardiovascular disease [40, 41].

The presence of CHIP contributes to the acceleration of atherosclerotic vascular lesions. This fact was confirmed in animal models, and similar conclusions were obtained for humans [41–43]. The mutations characteristic of CHIP accelerate the atherosclerotic process, which was noted even under a slight increase in their allele load [41]. An experimental model of CHIP in mice showed that an atherosclerotic lesion of the aorta was 60% more pronounced in the experimental animals compared to the control group [43]. Such modeling of CHIP showed its exceptional reproducibility in other animal experiments [43, 44]. Similar results were obtained when modeling CHIP associated with *JAK2V617F* mutation. The presence of this mutation in animals caused an increase in erythrophagocytosis in atherosclerotic plaques, which accelerated their destabilization [45]. In addition, this mutation was associated with a higher frequency of thrombosis in atherosclerotic plaques [45, 46].

Clonal hematopoiesis of indeterminate potential increases not only the risk of acute cardiovascular events, but also aggravates the course of heart failure (HF) [40, 45]. In a study by Sano S et al., mice were transplanted with 10% Tet2-/- BM cells, and the association of inactivated driver gene with high incidence of HF development was found [43]. A detailed transcriptomic analysis of heart tissues in animals demonstrated an increased expression of NLRP3-inflammasome-related genes, as well as IL1B gene. The use of NLRP3 inhibitor decreased the incidence of cardiac remodeling and the risk of developing HF in mice [44, 47, 48]. Thus, driver mutations of CHIP were demonstrated to intensify the proinflammatory response leading to the development of cardiovascular pathology [7, 45, 48].

At the same time, new data continues to emerge, stimulating further studies regarding the role of CHIP in the development of various variants of the course of type 2 diabetes [7], Alzheimer’s disease [7, 49], autoimmune diseases [7, 50], thrombosis [7, 46], and other pathologies. The decisive role in somatic pathology is attributed to the combination of effects of somatic mutations characteristic of CHIP with chronic inflammatory process, prolonged hyperactivation of the immune system, concomitant pathology and its therapy, lifestyle, as well as the impact of external factors [46].

Ionizing radiation as an inducer of genetic instability and clonal hematopoiesis

The action of IR leads to disruption of repair processes, interphase or mitotic reproductive cell death, and increasing deficit of differentiated cells with the formation of deterministic effects of irradiation. The latter consist in the direct damaging effect of IR on cells and tissues, manifesting themselves only after irradiation above the threshold dose with clinically significant consequences, both deterministic (tissue reactions) and stochastic. The degree of damage severity increases rapidly as the radiation dose accumulates. [51, 52].

When exposed to low-dose IR, stochastic effects develop. Low doses in this case are commonly understood as follows: a single equivalent dose of up to 0.1 Sv or 10 rem; an absorbed dose of up to 0.1 Gy or 10 rad; an effective equivalent dose of up to 0.1 Sv/year, which approximately corresponds to the exposure dose of 750 μ R/h [1, 6]. In case of such exposure, when an insignificant damage to cells under the IR influence occurred but was completely eliminated by regenerative processes, the cells retain viability but acquire genetic mutations. The probability of such damage at a single exposure to low doses of IR is minimal, although sharply increasing with increasing the effective equivalent dose and duration of exposure. Consequently, stochastic effects are characterized by the absence of a dose threshold and are assumed to occur with a probability linearly proportional to the influencing IR dose. Stochastic effects include the development of MBD and solid tumors, as well as hereditary pathologies [4, 6, 51].

Thus, the main reaction of the body to the chronic effect of low-dose IR is a disorder of genome stability and regulatory processes. In the setting of genetic instability, various reactions of the organism to the impact of external factors, up to death, are possible. An increase in the number of

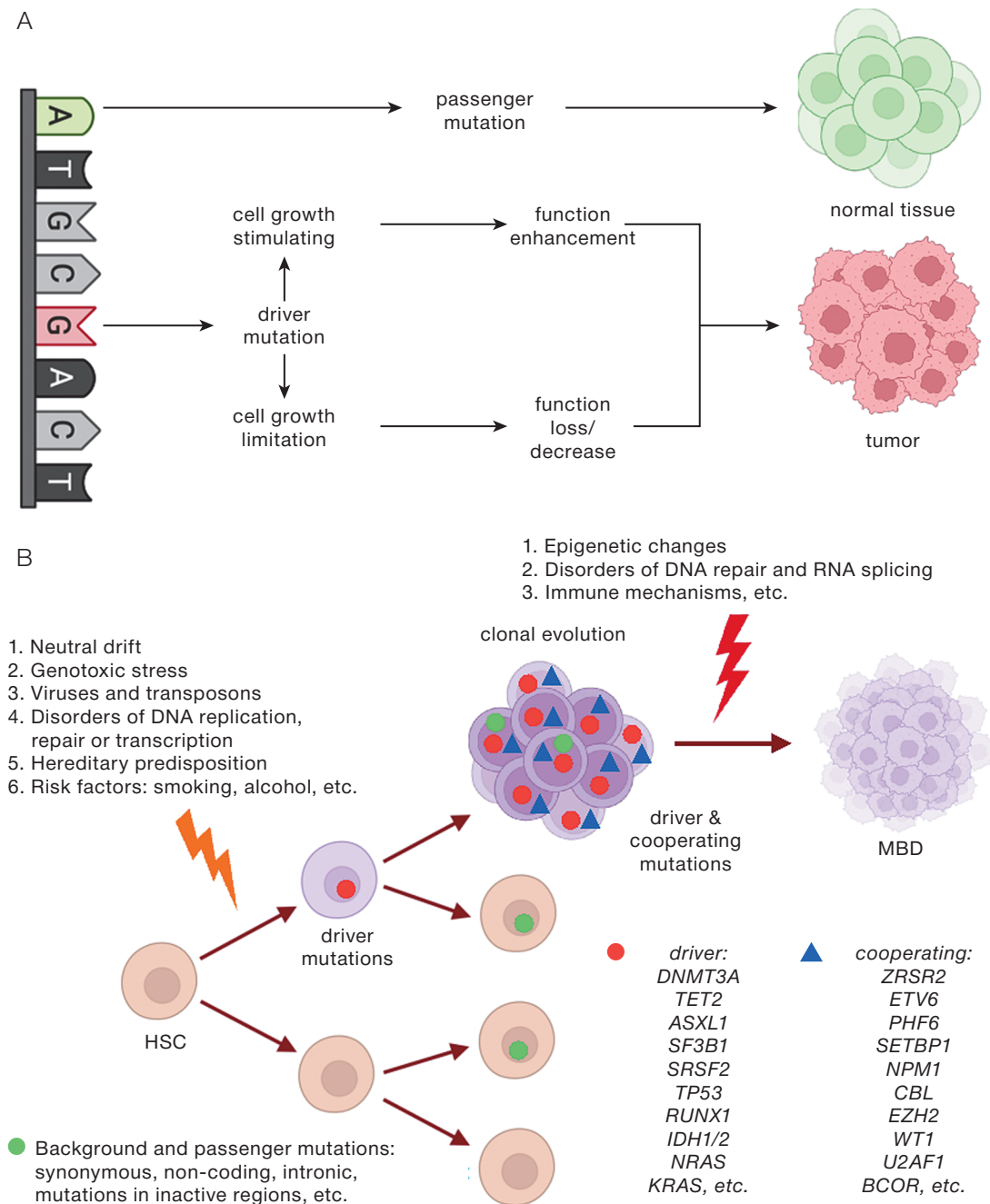


Figure prepared by the authors using data from [24]

Fig. 1. Model of clonal hematopoiesis: realization of passenger (A) and driver (B) mutations activity

chromosomal aberrations may precede the development of secondary immunodeficiency, premature aging, neoplasia, including MBD, as well as somatic pathologies. Low-dose IR is a stress factor for the organism, with the distant consequences of its long-term chronic exposure consisting in the depletion of compensatory capabilities of the organism [7, 52].

The number of publications on occupational exposure effects, including low-dose IR in a certain professional contingent (workers in the nuclear industry, radiologists, etc.) is currently growing. In this regard, a study by Jasra S et al published in 2022 seems noteworthy. The researchers analyzed the effects of chemical substances and dust particulate matter on 481 rescue workers involved in combating

the disaster in the World Trade Center on September 11, 2001. A significant increase in the CH risk in these individuals was determined, with the most frequent mutations affecting the *DNMT3A* and *TET2* genes. The frequency of their detection increased with age in comparison with 255 employees from the comparison group [53].

Another large-scale study, conducted in 2019 among atomic bombing survivors without an MBD diagnosis, found the radiation influence to result in blood cell clonal expansion. This led to a long-term increase in circulating monocytes in the group of people older than 60 years [54]. Also in 2022, the results of a study analyzing the presence of CH driver genes mutations in NASA astronauts were published. The study identified 34 nonsynonymous

mutations in 17 driver genes, with the highest frequency of occurrence in the *TP53* and *DNMT3A* genes [55].

A recent research focus has been the occupational IR impact on oncologic and cardiovascular pathologies in employees of the nuclear industry and radiologists. Thus, a large meta-analysis found the absorbed IR dose, above which the mortality from circulatory system diseases in these categories of workers increases, to be equal to 0.5 Gy [56].

A meta-analysis study (data from 15 countries) on the total mortality and mortality from all malignant neoplasms for workers in the nuclear industry, as well as for workers in contact with the most toxic heavy metals and chemical compounds, revealed no obvious increase in mortality from all malignant neoplasms compared to the population [57]. In a meta-analysis of data on the risks of cardiovascular pathologies, the authors also noted no significant differences with the population [58]. However, in the context of the effect of low-dose IR on the CH in these categories of individuals, no information is currently presented in large-scale works on the identification of mutations associated with CH. The majority of domestic studies are centered around the characteristics of IR and a retrospective analysis of morbidity, as well as the survival of employees exposed to long-term low-dose IR. Consequently, the possibility of identifying mutations associated with CH is of greatest interest for current research.

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CONCLUSION

To date, the association of CH with natural aging processes has been well established. The influence of CHIP on the increased risk of hemoblastosis, somatic pathology, and overall mortality has been documented. Genetic instability in the *DNMT3A*, *TET2*, *ASXL1*, *JAK2*, *TP53*, *PPM1D*, *SF3B1*, and *SRSF2* genes, which most often initiate CH in combination with chronic inflammation and increased immune activation, is associated with these diseases.

At the same time, there is a lack of comprehensive information on the risks of transition of clinically silent CHIP into disease. Timely screening aimed at identification of factors correlating with unfavorable outcomes can facilitate timely identification of people with an increased risk of pathology development.

Research into the influence of radiation-induced genetic instability on the formation of clonal expansion is relevant for health monitoring and preventive diagnosis of oncohematological and somatic pathologies in individuals with long-term low-dose anthropogenic exposure (nuclear industry workers and radiologists).

Further studies should elucidate the role of CH and CHOP in various pathologies, determining the possibilities of therapeutic effects aimed at preventing unfavorable course of the disease and increasing life expectancy.

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