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THE ROLE OF GENE AND STRUCTURAL MUTATIONS IN THE PROGRESS OF RADIATION-INDUCED MUTAGENESIS

Abstract

As realized by mechanisms of carcinogenesis was achieved sufficient progress and compiled huge material that is reflected in selected articles. On a par proto-oncogenes are low-level, their protein products in healthy cellules are participate in regulation of apoptosis processes, proliferation, cell cooperation, regulation of signaling inside the cellule. Radiation effects causing the mutations one of gene allele is factor into neoplastic cellule transformation that cause chromosomal rearrangements and proto-oncogenes amplification. Such mutations studying is represents solitary interest for radiation biology and medicine and enlarging our knowledge in the field of mutagenesis.

Key words: *gene mutations, radiation-induced mutagenesis.*

In recent years was achieved substantial advance in understanding of carcinogenesis mechanisms. Collected the huge factual material which is testified of identify role of genetic cellule apparatus changes. Collected data were time and again systematized in some articles [1-2]. Basis facts which are confirm the ideas about carcinogenesis as of progressive mutation replenishment process are recited below in alphabetical order and boiling down to the following:

- first of all, most of mutagens are carcinogenesis;
- secondly, in the cellules of malignant tumors are observed numerous locus-specific mutations;
- thirdly, genetic burden to the progress of malignant tumors is based on presence of terminal mutations in specific locus responsible for maintenance of genetic instability;
- the fourth, transgenic animals having the specific mutation of any gene aligned with malignant transformation is characterized with extremely high probability of swelling progress at an early age. Experiments results with such animals are the evidence of mutation role in carcinogenesis process.

Events resulting in swelling uprising are clear on molecular level. It is known that for malignant swelling uprising is necessary from 3 till 7 mutations in prorated genes of the same cellule [3-4].

Genes which take part in carcinogenesis are fall into two classes: oncogenes and genes – suppressor of swellings. Mechanism of its concern in malignant transformation are exactly opposite. Oncogenes are promotes degeneration in the time of expression rising and genes – suppressor in the time of reduction or absolute stopping. In health, oncogenes are in comparatively low-level condition that is way they called proto-oncogenes. Protein product of its genes in health cellules are have a hand in apoptosis regulation processes, proliferation, cell cooperation, regulation of signaling inside the cellule. It is recognized that the number of proto-oncogenes is near to natural limit determining by key point of known biochemical processes in cellules [5]. When the number of its proteins is increase because of mutation of one of gene allele the cellule is exposed to neoplastic transformation. Such active mutations may be the result of chromosomal rearrangement or proto-oncogenes amplification.

Strongest available evidence about the concern of point mutation in oncogenes activation in result of chromosomal rearrangement is formation of Philadelphia chromosome in the time of myeloleucosis. In such a manner the reciprocal translocation 9:22 is registers in 95% of given leucosis cases. Amplification of proto – oncogene is typical for genes of MYC. For example, oncogene NMYS in case of neuro and retinoblastoma is demonstrates the maximal copy number – to 200 on haploid cellule gene.

Swelling genes suppressors are coding the proteins working as negative regulators of cellular processes such as intracellular signaling. Also, they are regulates transcription, apoptosis, DNA repair etc. For malignant transformation is necessary the abolition of function of output or extinction from the cellule that is caused by mutation of both gene allele. Such mutations are called inactivated. As known if the cellules are unable to find out either DNA damage, for example, in consequence of terminal mutation BRCA-1 BRCA-2 genes, than carrier of such mutation have the progressing of malignant swelling. In the first instance - most probably T- cellular lymphadenoma or leucosis, in the second, mammary cancer. If the cellules are unable to liquidate known DNA damage the result will be the same.

Shining examples are the cases of hereditary polypous colorectal cancer. Terminal mutation is touch on one of unpaired DNA bases genes.

Finally, if the cellules are unable to start process “autocide” in the time of DNA damage it is also lead to serious consequences for organism. Its confirmation is the faces with Li-Fraumeni syndrome having the terminal gene mutation p53 which product is occupy central place in apoptosis regulation. Apoptosis abnormality because of p53 mutation is leads to cellules keeping with DNA damage and at long last closely in evitable the uprising of different swellings and most of them at an early age [6].

Altogether, carcinogenesis and radiation induced are presenting as sequential process. At least, point 4 stages: actuation, conversion, progression. Two stages passing are reliant on specific genes mutations and on epigenetic genes changes. Decides, that tumor responses of radiation are connected with mutagenic action at the stage of actuation. Acting on the stage of conversion the ray treatment will aggravate malignant transformation. We may suppose that radiation induced-evoke genome instability can make a contribution to replenishment mutation process which are leads to malignant transformation. At that, the value of its phenomenon may be very big in the time of radiation effects in the small doses.

Therefore, absolute interest represented by the skills of San – Francisco university employees testifying to possible role of radiation induced genome instability in malignant cellules transformation [7].

Authors were exposed to gamma irradiation on the dose of 3 gr. primary culture epithelial cell lacteal gland of mice and than, during 30 generations analyzed the periodicity of chromatid aberration. Rising number of chromatid aberration right after influence was came down to control stage

and then in 15-20 generations began increase and in final total exceed in 1,5 times the aberration number evoking with direct effect of radiation. It is important to note that the effect had depended on hereditary trait of organism. In cellules culture BALB/c the instability was well expressed and in the case of C57BL/6 – there wasn't. Notable, that these lines of mice are forceful differs with periodicity of radiation induced cancers of lacteal gland. The mice BALB cancers lines are have considerably larger than on C57BL.

Which the DNA damages in the time of radiation are important for carcinogenesis? Such authoritative international organization as SCAAR UN has lately came to conclusion that the main mechanism by dint of which the radiological damage leads to the malignant swelling progress is loss of critical genes – suppressors [8]. Proto-oncogene activation is supports of less importance role but for some swellings have vital importance. Suppose that radiation induced inactivation of genes – suppressors is derives by the way of deletions and proto-oncogene by the way of point mutation or chromosomal rearrangement. Not any genetics changes specified for radiation induced swellings is not described.

In such a manner, the uprising of malignant swellings is aligned with replenishment of different mutations and possibly, epigenetic changes in somstical cells. There is no room for decide that in the time of ionizing radiation acting the situation is different now. As is known, increased risk of malignant neoformation progress is one of principal distant radiation exposure. Diagnoses of carcinogenic risk are based on monitoring results of injured due to bombardment of Hiroshima and Nagasaki. More than 50 years has passed from the date of accident but up to now the specialists has no agreement of opinion on many questions and the most principal –about form of dependence dose – effect. Evident, that the reasons of such uncertainty aligned not only with well-known difficulties of epidemiological analyzes but and deficiency of faithful representation about biological mechanisms of carcinogenic activity of ionizing radiation in low doses. Currently, radiobiological community in the name of official organizations, such as SCAAR, US Department of Energy is agrees with linear dependence for induction of solid tumors and linear-quadratic for leucosis. Here with, checks out that these dependences are more or less acceptable compromise with today knowledge level [9].

Biggest disputes offers the field of low doses where according to some reports possible more high output of malignant swellings on dose unit than in the time of big doses [10].

There is just the opposite assumption about the existence of boundary carcinogenic activity of ionizing radiation [11].

Solution to a question about the dependence form dose – effect have principal value and far-reaching consequences just as theoretical as and practical attitude.

For example, predicted numbers of cancerous diseases associated by Chernobyl accident differs more than 10 times by estimate in using of different mathematical models [12]. While we can take note that today's knowledge is not enough for exact process understanding which are happens in the time of ionization radiation in low doses acting. Therefore tumor responses of ray treatment are intricately to estimate and predict. Apparently, molecular mechanisms researches of carcinogenesis and singularities of this process in the time of ionization radiation in low doses acting is promising approach to assist the decision of the problem. Take into account the key role of the mutation in malignant transformation one must admit that mutation researching in body cells is presenting one of these approaches.

Ionizing radiation is considers as universally mutagen. Experimental researches on plants and animals have indicated that radiation may induce the hereditary effects and unlikely, that people are the exclusion in this case. For estimation of genetic risk are using two assumptions:

1) that 7 "specific" gene locus are composing appropriate basis for extrapolation on genetic abnormalities by people;

2) that inherited mutations are induces by radiation damages in genome with linear dose dependence.

There is noting the next at the report of MCRD [13]: "There are still no direct evidences that radiation of parents is comes to abundance of hereditary diseases. Commission is attests that there are the evidences of hereditary genetic effects of radiation by animals. Therefore the Commission is continuing to include risk of hereditary genetic effects in radiological defense system". Researches on mice are continue using for estimation of genetic risks in view of evidence deficiency by people that hereditary mutations are causing genetic effects of posterity. Finally, there is similar and final conclusion on the page 154 [13]: "there are no direct evidences conditioned with radiation of inherited abnormalities, the facts on experimental animals are provides unanswerable reasons to continue using genetic approaches for estimation of these risks".

There is no reliable information about inherited genetic effects by people with radiation of parents: "Many epidemiological researches were unable to find out the evidences of radiation effects by parents before impregnation as with the descendants which are survived after the atomic bombing in Japan so and with workers which were exposed to radiation. We haven't found the conclusive evidence pointing out that ionizing radiation may to eventuate implementing the increase of childhood cancers incidents". It is clear, that if the effect will induced with rate of 0,2 – 0,5% of ambient level even for dose of 1 gr. than epidemiology of small and average doses will require the unreal size of cohort. In this results began the search of more sensitive methodical approaches which in 1999 were realized in the mutation research in minisatellite DNA repeats [15-16].

Tandem DNA repeats (satellites) are components of all eukaryotic genomes. In terms of length differs microsatellites (2-6 pairs of basis) and minisatellites (6-100 pairs of basis and more). Usually, the minisatellites equences are tops from 500 to several thousands of pair basis. Because of polymorphism endwise being the result of variations in repeat numbers and some of satellites ability to range in the time of cross hybridization with tenner of other locus in genome the minisatellites may by individually identified on DNA-fin-gerprints [16-17].

Micro – and minisatellites are not encoding the succession that's why for them is signify the selective neutrality. Exact functions of minisatellites are not educed through and through. Nevertheless, there are assumptions of mechanisms because of which the satellite repeats are participates in the work of coding genes [18] changing the allied genes expression.

Since the advent of radiation genetic of man (researches beginning in Japan) 60 years have passed. Nevertheless, there are no any unambiguous data about registered hereditary genetics effects by people. As the alike effects time and again proved for other objects of animality and the human is shouldn't be exclusion, it is confesses that relating to human cohorts inherited changes by descendants of radiation parents may escape analyses. That is caused by following factors:

- Low mutation rate of coding genes by mammals (about 10^6on the gene in generation;
- High accumulated basal level of mutation changes in human population on the back of which is difficult to find out small increases of exponent for radiation cohorts;
- Singularities of oligocarpous pregnancy by large mammals (and human) in the time of which the genetic

anomalies are eliminates on at early progress stages and inaccessible for register.

All that makes low-probability identification over the back ofexponentincrease which would expect with any real selection of radiation people descendants. Need very big cohorts counting tenner- hundreds thousands of children even with the doses by parents from above small (small doses – to 0,1 gr., according to ICRD and BEIR, ant to 0,2 gr. according to SCAAR). According to standardize world estimated risk of hereditary violations and pathologies with the radiation of parents in the dose of 1 Gr. the assessed risk is amount from 0,2% to 0,54 % over the ambient level of exponent [19-20].

Current idea about the genetic sequels of ionizing radiation action on body cell of human in-vivo is based on the results of cytogenetic analysis of structural mutations. At once, virtually from the date of formation of radiation genetics the radiation effect is induced many genetic material changes which are unable to be identified by dint of cytogenetic methods – mutations in single genes locus. For these reasons the radiation of such mutations is represents the solitary interest for radiation biology and enlarge our knowledge in the field of radiation mutagenesis.

However, until quite recently, the information about induce of gene mutation in body cells of irradiated persons was restricted HRPT – locus because of deficiency of other methodical possibilities. Progressing of molecular and cellular biology is considerable extending the methodical base for studying of somatic mutagenesis in similar locus.

In the next reviews will enumerate known researching methods of gene mutations in body cells of human which are admits to carry on investigation of big contingents.

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Резюме

РОЛЬ ГЕННЫХ И СТРУКТУРНЫХ МУТАЦИЙ В РАЗВИТИИ РАДИАЦИОННО-ИНДУЦИРОВАННОГО МУТАГЕНЕЗА

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В понимании механизмов канцерогенеза достигнут достаточный прогресс и собран огромный фактический материал, что нашло свое отражение в ряде сборных статей. В норме протоонкогены малоактивны, их белковые продукты в здоровых клетках участвуют в регуляции процессов апоптоза, пролиферации, межклеточного взаимодействия, регуляции передачи сигналов внутрь клетки. Радиационное воздействие, вызывая мутации одного из аллелей гена, приводит к неопластической трансформации клетки, что вызывает хромосомные перестройки или амплификацию протоонкогена. Изучение таких мутаций представляет отдельный интерес для радиационной биологии и медицины, и расширяет наши знания в области мутагенеза в целом.

Ключевые слова: *генные мутации, радиационно-индуцированный мутагенез, онкоген.*

Тұжырым

РАДИАЦИЯЛЫҚ – ИНДУЦИРЛЕНГЕН МУТАГЕНЕЗДІҢ ДАМУЫНДАҒЫ ГЕНДІК ЖӘНЕ ҚҰРЫЛЫМДЫҚ МУТАЦИЯЛАРДЫҢ РОЛІ

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Канцерогенездің механизмдерін түсінуде жеткілікті прогресске жетті және үлкен нақты материалдар жиналды, ол бірнеше жинақталған мақалаларда көрініс тапты. Протоонкогендер нормада аз белсенді, олардың ақуыз өнімдері сау ағзалары апоптозда, пролиферацияда, ағзааралық өзара әрекеттесулер процесстерін реттеуге, ағза ішіндегі дабылдарды жіберуді реттеуге қатысады. Радиациялық әсер геннің аллелейдерінің біреуінде мутациясын шақыра отырып, ағзаның неопластикалық трансформациясына әкеледі, ол хромосомалық қайта құруға немесе протоонкогеннің ампликациясына ұшырайды. Осындай мутацияларды зерделеу радиациялық биология мен медицина үшін жеке қызығушылық танытады және жалпы мутагенез саласындағы біздің білімімізді кеңейтеді.

Негізгі сөздер: *генетикалық мутациялар, радиациялық-индукциялық мутагенез, онкогендер.*

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ИЗУЧЕНИЕ ПОКАЗАТЕЛЕЙ ТОЛЩИНЫ СТЕНКИ ЛЕВОГО ЖЕЛУДОЧКА ПРИ АРТЕРИАЛЬНОЙ ГИПЕРТЕНЗИИ В РАЗЛИЧНЫХ ЭТНИЧЕСКИХ ГРУППАХ

Аннотация

В последние годы при исследовании артериальной гипертензии, большое внимание обращается на ремоделирование сердечно-сосудистой системы. При изучении артериальной гипертензии (АГ), отмечено, что происходит прежде всего ремоделирование левого желудочка сердца, связанное не только с возрастом, но и с этнической принадлежностью.

Методы и результаты. Проведено ретроспективное исследование случай-контроль, по данным патологоанатомических протоколов вскрытий, проведенное в г.Семей Республики Казахстан умерших за 13 лет, страдавших при жизни артериальной гипертензией.

Выводы. Имеются возрастные различия среди групп умерших, более молодой возраст отмечен в группе казахской популяции, в сравнении с русской популяцией. ГЛЖ I степени выражено в большей степени в группе казахской популяции (65,1%) по сравнению с русской (49,3%). ГЛЖ II степени выражено в большей степени в группе русской популяции (50,4%) по сравнению казахской (34,2%). Отмечены этнические различия в толщине стенки левого желудочка, более выраженные в группе русской популяции. В возрастной группе 40-49 лет различий по толщине стенки левого желудочков по национальному признаку не выявлено. В возрастной группе 50-59 лет выявлены различия по толщине стенки левого ($p<0,025$) желудочков по национальному признаку, более выраженные в группе русской национальности по сравнению казахской.

Ключевые слова: *патологоанатомическое исследование, артериальная гипертензия гипертрофия левого желудочка, гипертрофия правого желудочка, этническая принадлежность, ремоделирование.*

В последние годы при исследовании артериальной гипертензии, большое внимание обращается на ремоделирование сердечно-сосудистой системы. При изучении артериальной гипертензии (АГ), отмечено, что происходит, прежде всего, ремоделирование левого желудочка сердца, связанное не только с возрастом, но и с этнической принадлежностью.

Материал и методы исследования. Проведено ретроспективное исследование случай-контроль, по данным патологоанатомических протоколов вскрытий, проведенное КГКП «Патологоанатомическое бюро» г.Семей Восточно-Казахстанской области республики Казахстан и Семейского филиала РГКП «Центр судебной медицины Министерства здравоохранения Республики Казахстан» умерших за 13 лет (начиная с 1999 года по 2011 годы), страдавших при жизни артериальной гипертензией.

В группу включения для проведения анализа вошли, данные протоколов вскрытия умерших остро в результате нарушения мозгового кровообращения, смерти от острого инфаркта миокарда в течение суток, смерть при острой хирургической патологии органов брюшной полости. Критериями не включения в анализируемую группу были: наличие заболевания органов дыхания, пороки сердца, ожирение, сердечная недостаточность. Таким образом, были отобраны протоколы вскрытий умерших, у которых при жизни, помимо АГ, не было сопутствующей патологии, самостоятельно приводящей к ремоделированию правого желудочка. Статистическая обработка проводилась с использованием пакета прикладных программ (ППС) STATISTICA фирмы StatSoft Inc. (США).

Всего было отобрано 537 протоколов вскрытия, из них составили мужчины – 223 (42%), женщины – 314 (58%).

Для проведения анализа имеющих данных в исследуемой группе взяты следующие значения, определяющие параметры левого и правого желудочка на момент вскрытия. За нормальную толщину стенки левого желудочка (без папиллярных мышц)