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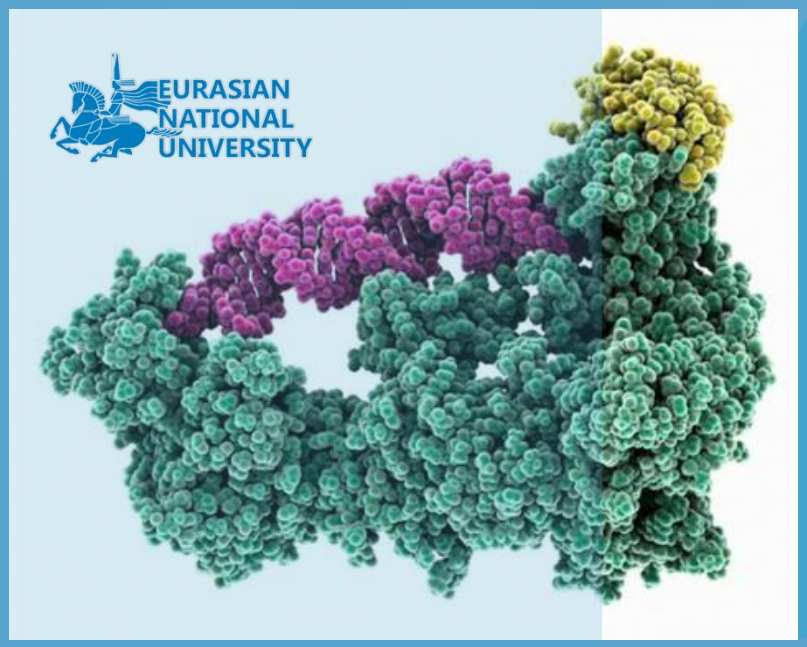

Л.Н. ГУМИЛЕВ АТЫНДАҒЫ
ЕУРАЗИЯ ҰЛТТЫҚ УНИВЕРСИТЕТІ

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Жинақ «Омаров оқулары: XXI ғасыр биология және биотехнологиясы» атты халықаралық ғылыми форумына қатысушылардың баяндамаларымен құрастырылған. Бұл басылымда биология, биотехнология, молекулалық биология және генетиканың маңызды мәселелері қарастырылған. Жинақ ғылыми қызметкерлерге, PhD докторанттарға, магистранттарға, сәйкес мамандықтағы студенттерге арналған.

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Клиникалық жағдайларда қолдануға рұқсат етілген кез келген емдеу әдістеріне дейін гендерді редакциялауға және генетикалық модификацияға қатысты этикалық мәселелердің жан-жақты ескерілетініне көз жеткізу өте маңызды.

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INFLUENCE OF P53 PROTEIN ON THE HUMAN REPAIR SYSTEM

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Genetic stability and variability in the cellular genome are determined by the coordinated operation of mutator and anti-mutator genes, the regulatory genetic elements responsible for key matrix processes. Spontaneous mutation is a hereditarily fixed trait and has a relatively constant rate in each species or cell type. This mutation rate is maintained by defense systems at the cellular and organismal levels, so it is usually low in eukaryotic organisms. However, anthropogenic environmental pollution can lead to an accumulation of mutations in the human genome, which can increase the frequency of hereditary and somatic diseases, reduce longevity and the probability of leaving offspring[1]. Which brings us to an introduction to the tumor suppressor gene, p53. It is the most common target for genetic changes in cancer, with mutations occurring in about 50% of all human tumors. Mutants of p53, which lack DNA-binding activity and therefore transcriptional activity, are among the most common mutations in human cancer. Recently, a new role for p53 has been discovered because the tumor suppressor is also involved in DNA repair and recombination. In cooperation with its function in transcription, the transcription-independent roles of p53 contribute to the control and efficiency of DNA repair and recombination[11].

The p53 protein is a transcription factor that is a key player in the human cellular repair system. It controls many cellular processes, including apoptosis (programmed cell death), DNA replication, and DNA repair. The tumor suppressor p53, a tetrameric protein that can bind to specific DNA sequences and activate gene expression, plays a central role in the cellular response to oncogenic events. p53 can induce cell cycle arrest in response to DNA damage and thus can prevent genetic changes such as chromosomal rearrangements and gene amplifications. In addition to responding to DNA damage, p53 can also induce apoptosis in response to the activation of oncogenes such as c-Myc and ElA[2].

The p53 protein has several domains. Oligomerization appears to be necessary for tumor suppressor activity of p53 because p53 mutants deficient in oligomerization cannot suppress the growth of carcinoma cell lines. The monomer, which consists of a β-chain and an α-helix, binds to a second monomer via an antiparallel β-sheet and an antiparallel helix-helix interface to form a dimer. Two of these dimers bind through the second and distinct parallel helix-helix interface, forming a tetramer[2]. The p53 DNA binds as a tetramer, and each subunit recognizes five nucleotides of a 20-nucleotide long stretch of DNA. Conformational shifts in the oligomerization domain extending to binding domains regulate DNA-binding activity, but do not affect the stoichiometry of the p53 subunit. Interestingly, conformational shifts in p53 can still allow it to retain its function by participating in DNA protection. In the study, one such mutant was the murine equivalent of human histidine 273, which is often associated with human tumors[3]. Mutations in the p53 molecule are most commonly found in the DNA-binding domain at specific hot spots such as codons 175, 245, 248, 249, 273 and 282. However, the spectrum of mutations can vary depending on the type of tumor and the cause of the tumor. For example, lung cancers are most commonly associated with mutations in codon 145, while mutations in codon 249 are characteristic of hepatocarcinomas caused by aflatoxin B. Also, the pattern of mutations may differ depending on whether the substitution of an amino acid residue is a transversion or a transit[19]. In general, the p53 protein plays an important role in DNA repair in human cells, and its activation is important for maintaining genomic integrity. If p53 is missing or does not function properly, it can lead to an increased frequency of mutations that can lead to the development of cancer and other diseases. For example, people with hereditary Li-Fraumeni syndrome (Li-Fraumeni syndrome), which is associated with a mutation in the TP53 gene, have a significantly increased frequency of cancer development[22].

Table 1. Multiple modes of p53 disruption in human cancer.

Mechanism of inactivating p53	Typical tumours	Effect of inactivation
Amino-acid-changing mutation in the DNA-binding domain	Colon, breast, lung, bladder, brain, pancreas, stomach, oesophagus and many others	Prevents p53 from binding to specific DNA sequences and activating the adjacent genes
Deletion of the carboxy-terminal domain	Occasional tumours at many different sites	Prevents the formation of tetramers of p53
Multiplication of the MDM2 gene in the genome	Sarcomas, brain	Extra MDM2 stimulates the degradation of p53
Viral infection	Cervix, liver, lymphomas	Products of viral oncogenes bind to and inactivate p53 in the cell, in some cases stimulating p53 degradation
Deletion of the p14^ARF gene	Breast, brain, lung and others, expecially when p53 itself is not mutated	Failure to inhibit MDM2 and keep p53 degradation under control
Mislocalization of p53 to the cytoplasm, outside the nucleus	Breast, neuroblastomas	Lack of p53 function (p53 functions only in the nucleus)

After becoming familiar with its composition and possible mutations, we can begin to get acquainted with the functions of such an important protein. It has quite a few of them, given that we still don't know the full list of all p53's capabilities at this point. It targets genes responsible for global genomic repair (DDB2 and XPC) and unpaired nucleotide repair (MSH2, PCNA, MLH1 and PMS2), and induces DNA polymerase η to repair damage near the replication fork. Finally, p53 induces the p53R2 gene, a structural homologue of ribonucleotide reductase, which is important for maintaining nucleotide precursor stores during DnA repair [4].

For p53 to initiate a sequence of events that will lead to either inhibition of cell cycle progression or programmed cell death, it must recognize and bind to its consensus DNA recognition (RE) elements. Typically, p53 consensus REs are located near the target genes several thousand base pairs away from the transcription initiation site. In addition, p53 target genes often have at least two widely spaced consensus p53 REs[5]. p53 can also recognize REs whose structure differs somewhat from the consensus RE. For example, p53 is weakly induced by AQP3, in which the RE consists of three pentamer pairs[6]. Notably, among the genes regulated by p53, their respective levels of activation or inhibition of transcription vary greatly. This is due, at least in part, to variations within individual p53 REs[7].

There are several views on the mechanism by which p53 can promote transcription. The first is based on the assumption that the promoter region of the gene activated by p53 is normally inaccessible to common transcription factors and RNA polymerase. In this scenario, p53 binding to its RE in the promoter would promote promoter opening through recruitment of either chromatin remodeling factors (CRFs)[8] or histone transacetylases (HATs) and/or methyltransferases[9]. This view has recently been confirmed in a significant number of studies.[8-12] The physical and functional interactions between p53 and p300 HATs are well documented. The involvement of methyltransferases PRMT1 and CARM1 in p53 function has also been demonstrated in an in vitro study using a chromatin matrix with GADD45 p53 RE,[13] thus histone modifications and subsequent changes in chromatin structure and function appear to be a major outcome of p53 binding to RE. Likewise, a study[14] showed that the large monkey virus T antigen 40 inhibits p53-mediated transcription by blocking the ability of p53 to bind to promoters that are sensitive to it. In contrast, p53 stimulates transcription by enhancing the recruitment of TFIIA and TFIID to the promoter and inducing conformational changes in the DA complex. The DA complex is resistant to T-antigen repression when the TFIID-DNA complex is formed before the addition of the p53-T-antigen complex, indicating that the T-antigen targets TFIID. In addition, the p53-T antigen complex prevents the TATA-binding protein from binding to the TATA box, which provides insight into the mechanism of not only the protein itself, but also how viruses learn to bypass this line of defense. For all that, the importance of p53 functions independent of transcription cannot be underestimated.

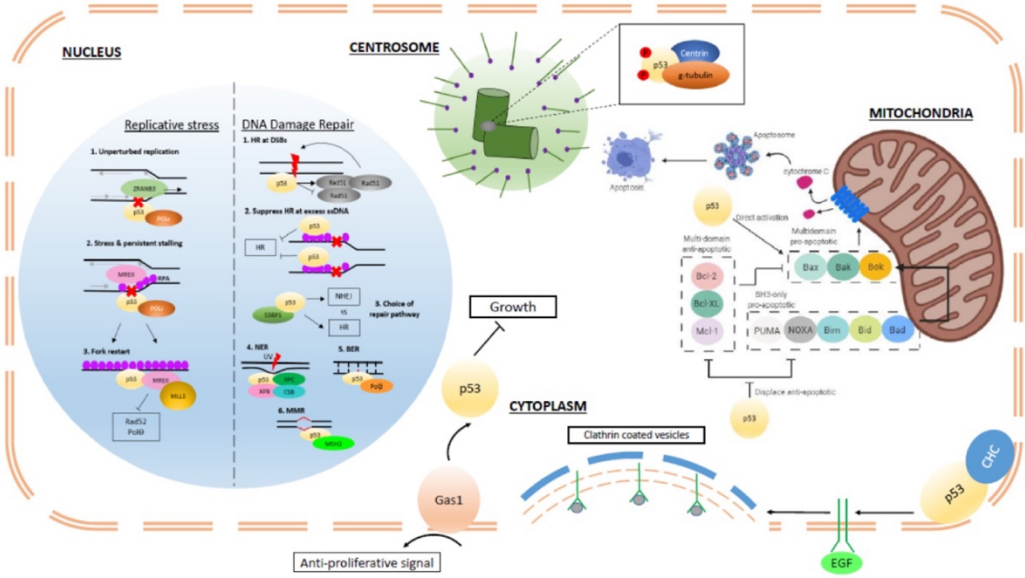

Figure 1: Functions of p53 independent of transcription

Within the nucleus, p53 regulates fork dynamics and processivity in response to endogenous and exogenous replicative stress through interactions with other key factors such as MRE11, replication protein A (RPA) and transfusion polymerases. (Gray arrows: direction of replication mechanism; black arrows: direction of ZRANB3 translocase complex; red cross: replication blockade; red lightning: DNA damage (double-stranded or single-stranded). In the presence of damaged DNA, p53 regulates various repair mechanisms, such as homologous recombination (HR), by limiting excess recombination through interactions with Rad51 and RPA, and nucleotide excision repair (NER), base excision repair (BER) and mismatch repair (MMR) through interactions with relevant components of the respective pathways, as shown. In the cytoplasm, p53 binds to centrosomal proteins such as centrin and g-tubulin in regulating centrosomal homeostasis and preventing reduplication (red P: posttranslational phosphorylation). By interacting with clathrin heavy chains (CHC) on the plasma membrane, p53 can regulate EGFR endocytosis and therefore modulate the effects of g Cell Growth Factors on growth and proliferation. Inside mitochondria, p53 can promote apoptosis by displacing anti-apoptotic members of the BCL-2 family and from BCL-2 and directly activate BAX or BAK to induce mitochondrial outer membrane permeabilization (MOMP)[18].

Several studies presented below have suggested that the acute response to DNA damage, which leads to activation of p53 transcription, cell cycle arrest and/or apoptosis, is not essential for tumor suppression. In tumor cells, the loss of p53 transcription-independent functions in damage perception, such as repair, may have a greater overall effect on tumor progression[18].

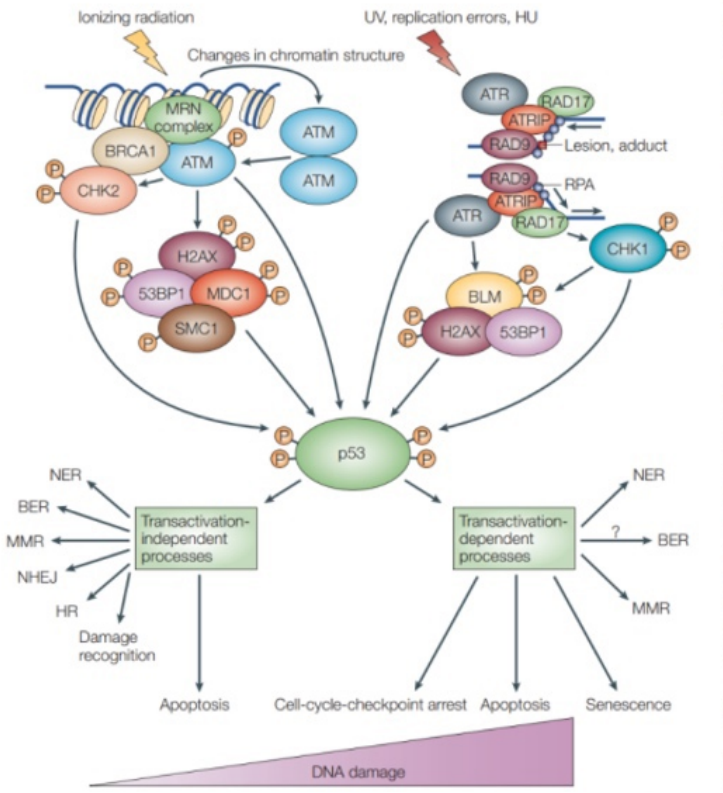

Figure 2. p53 functions as a "molecular node" in the DNA damage response

When a cell is stressed, such as DNA damage, p53 is activated and forces the cell through an arrest cycle to prevent further deterioration of DNA damage or the spread of damage to daughter cells. At the same time, p53 also stimulates repair processes to restore DNA integrity. There are several mechanisms that regulate p53 activation and its interaction with other proteins in the repair system. One such mechanism is phosphorylation of p53 by other protein kinases, such as ATM and ATR, which activate it in response to DNA damage. The activated p53 can then bind to other proteins, such as Mdm2, and block their ability to degrade p53, allowing it to activate its repair function. Another mechanism that regulates p53 is its interaction with proteins such as BRCA1 and RAD51, which are involved in double-stranded DNA damage repair by homologous recombination. When p53 binds to BRCA1, it promotes DNA repair and also prevents the development of breast cancer. When p53 binds to RAD51, it also participates in DNA repair, but already in double-stranded damage through an ambiguous mechanism[23].

It is also worth noting that some viruses encode proteins that block the interaction between the retinoblastoma protein of the infected cell (Rb) and transcription factors of the E2F family, such as E2F-1. This frees E2F-1 to activate target genes necessary for cell proliferation. But it also leads to the production of the protein p14ARF, which affects the activity of MDM2 (a negative regulator of the p53 protein) and the subsequent stabilization of p53. This slows down cellular (and therefore viral) replication. Viruses counteract this cellular defense by producing proteins that inhibit p53 function. This predisposes infected cells to become cancerous[23].

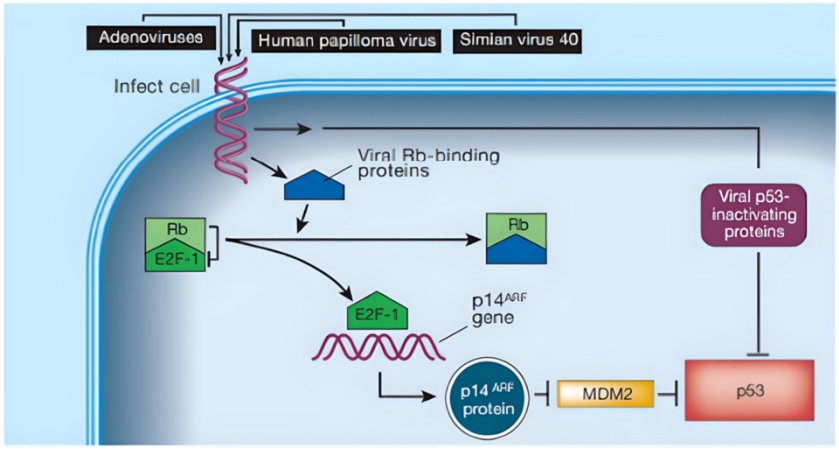

Figure 3: Viral oncogenes and the p53 network

DNA repair is an important process for maintaining the fidelity of the cell genome. It involves several pathways, such as excision repair involving nucleotide excision repair (NER) and base excision repair (BER), as well as mismatch repair (MMR) and double strand break repair (DSB)]. Each of these pathways uses a unique set of enzymes and mechanisms to repair the damaged DNA site. For example, in nucleotide excision repair, the damaged site is removed and replaced with a new nucleotide, and in base excision repair, the damaged base is removed and replaced with a new base. Mismatch repair is used to correct DNA replication errors, and double strand break repair is used to repair double strand breaks in DNA. Understanding these DNA repair pathways helps in the study of the causes of genetic diseases and the development of new treatments[15]. As a guardian of the genome, it is not surprising that the p53 family plays a role in DNA repair.The p53 family plays a role in DNA repair by participating in NER, which leads to the expression of genes such as GADD45, XPE and XPC. Mouse keratinocytes, similar to human keratinocytes lacking GADD45, show reduced thymidine dimer repair and increased sensitivity to UV radiation. GADD45 also interacts with histones and promotes chromatin relaxation by topoisomerase. The p53 XPC target gene involved in NER localizes to UV-induced damage regions, and its interaction with damaged DNA is enhanced by XPE[16]. Interestingly, the p53 protein itself is involved in both the NER and BER excision repair pathways. It was shown in a study[17] that p53 interacts with pol b DNA to stabilize the interaction between the damaged DNA and the BER mechanism. In mismatch repair (MMR), it was found that p53 interacts with the RAD51 promoter, albeit with little effect on its regulation[18]. There has also been a study[21] on how the DNA mismatch repair (MMR) system and p53 interact to maintain genome integrity in the presence of mutagenic stress induced by hydrogen peroxide. The results demonstrate that the effect of disabling p53 function is modulated by the effectiveness of the MMR system (and vice versa) and that there is an overlap between p53 and MMR system functions with respect to activation of apoptosis and mutagenesis after oxidative stress.

Due to the assumption that the central domain of p53 is involved in BER stimulation, a study[17] was conducted on the ability of two tumor-derived p53 mutants (R248W and R175H) to affect BER. For this purpose, purified baculovirus-expressed wild-type p53 was compared with purified baculovirus-expressed mutant p53 in both reconstructed BER and H1299 whole cell extracts. When the same amounts of proteins were added to the reconstructed BER reactions, the two mutant p53 proteins showed significantly reduced stimulation. When tested in H1299 whole cell extracts, the two p53 mutants could not stimulate BER at high protein concentrations alone, which may be due to the tendency of

mutant p53 to aggregate at high concentrations and the influence of some unknown factors in the cell.

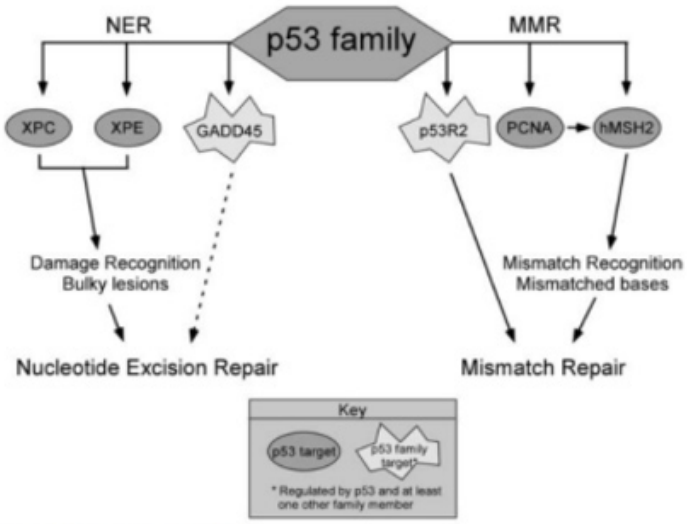

Figure 4 -DNA repair mediated by p53 family target genes

In an analysis of mutant p53 that is unable to elicit responses to acute DNA damage, the results show that p53 suppressor activity in various tissue types, including epithelium, is independent of its ability to respond to acute genotoxic strokes, and p53-mediated tumor suppression in lymphoma and fibrosarcoma caused by DNA damage was previously found to be independent of p53 ability to trigger responses to acute DNA damage. However, the results do not rule out the possibility that in nascent tumors p53 may respond to low-level chronic DNA damage caused by factors such as replication stress or telomere depletion by a different mechanism. The idea that the DNA damage pathway following chronic genotoxic stress may be mechanistically distinct from that following acute genotoxic damage provides potential resolution of controversies regarding the role of DNA damage signaling in p53 activation in incipient tumors and requires further investigation[18]. In general, we can say that the response of p53 depends on its subcellular localization in relation to the DNA damage site, the status of the cell cycle during DNA damage, and the duration of genotoxic stress. It can be assumed that when the degree of DNA damage is low, p53, whether unmodified or posttranslationally-modified, can interact with DNA repair mechanisms, either alone or in combination with other factors specific for repair. When the amount of DNA damage exceeds the level that p53 alone can successfully cope with, the tumor suppressor undergoes stabilization, which depends on posttranslational modification and functions as a sequence-dependent transcription factor. This activates a set of genes, mentioned in the studies above, that stop the cell cycle so that DNA repair processes can successfully repair the damage. At this stage p53 can also interact with and modulate various proteins specific to the repair process. If the DNA damage persists or is irreversible, p53 induces apoptosis-specific genes, leading to cell death [23].

The oncosuppressor p53 functions primarily as a transcription factor, as discussed at the beginning, and can mediate its various downstream functions by activating or repressing a large number of target genes. p53 is one of the most frequently mutated genes in human cancer, resulting in a mutant protein with an altered amino acid sequence, usually in the DNA-binding domain.

Table 2. The effect of p53 on DNA-repair and -recombination pathways.(CPD - cyclobutane pyrimidine dimers; ND -not determined; UV - ultraviolet light)

Pathway	**Type of damage**	**Damaging agents/cause**	**Dependence on p53-transactivation function**	**Dependence on p53-transactivation-independent function**	**Effect of p53 on process-specific protein(s) functions**	**Effect of process-specific protein(s) on p53 functions**
Nucleotide excision repair (NER)	CPD;(6-4)photoproducts	UV; cisplatin; 4-nitroquinolin oxide; and other oxidative damages	Yes	Yes	Yes	Yes
Base-excision repair (BER)	Single-base DNA damage(short-patch BER); single-strand break(long-patch BER)	Oxidizing, methylating alkylating, hydroxylating agents; lonizing radiation; spontaneous depurinations (short-patch BER) x-rays (long-patch BER)	Controversial	Yes	Yes	Yes
Mismatch repair (MMR)	Misrepaired nucleotides; insertion/deletion loops	Slippage of polymerasy during replication of repetitive sequences or recombinations; mutations in MMR genes	Yes	Yes	Yes	Yes
Non-homogolous end-joining (NHEJ)	Double-strand break	Lonizing radiation; chemical agents such as neocarziostatin	ND	Yes	Yes	Controversial
Homologous recombination (HR)	Double-strand break	Lonizing radiation; chemical agents such as neocarziostatin	No	Yes	Yes	Yes

Although four decades have passed since the initial discovery of p53, new and intriguing functions continue to be attributed to this crucial guardian of the genome.

Ultimately, p53's transcription-independent functions have been shown to be highly dependent on the degree of DNA damage, the stage of the cell cycle, and prevailing conditions such as mutational load and the presence of other oncogenes in a given cell. Nevertheless, despite the many studies on the mechanisms by which p53 regulates its targets, much remains to be learned about this amazing protein. Looking to the future, we see many new avenues to be explored, some of which will require new or more advanced technologies. Separating and accurately modeling such subtle contextual differences in a physiologically meaningful way will be important in determining exactly how p53 dictates cellular fate and outcomes.

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ЗЫҒЫР МАЙЫН ӨҢДЕУДІҢ БИОТЕХНОЛОГИЯЛЫҚ КӨРСЕТКІШТЕРІ

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Кіріспе. Майлы зығыр – көп мақсатты пайдалануға арналған бағалы ауыл шаруашылығы дақылы.

Зығыр - санитарлық мәдениет, оны себуден кейін егістіктерде патогендік инфекциялар мен зиянкестердің ең аз мөлшері қалады. Зығырды кез келген дерлік дақылдан кейін себуге болады, ал одан кейін кез келген дақылды орналастыруға болады. Бұл ауыспалы егістегі тамаша предшественник. Зығыр - бұл технологиялық мәдениет. Агротехнологияның элементарлық талаптары сақталса, ол жоғары экономикалық нәтиже бере алады. Оны өсіру үшін кәдімгі астық технологиясы, сондай-ақ дәнді дақылдарда қолданылатын құрал-жабдықтар (тұқым сепкіштер, жаттар, комбайндар) қолданылады. Бұл экологиялық таза мәдениет. Оны өсіру кезінде химиялық қорғаныс құралдары мен тыңайтқыштардың ең аз мөлшері қажет. Зығыр дақылдары топырақты ауыр металдар мен радионуклидтерден босатады. Ластанған жерлерден алынған зығыр тұқымдарында радиацияның ізі де жоқ. [1]

Соңғы кездері құрамында линолен қышқылының көп болуына байланысты емдік қасиеттеріне байланысты зығыр майын тағамға пайдалануға дүние жүзінде қызығушылық артты. Ол зат алмасуды жақсартады, денеден холестеринді кетіреді, қан қысымын қалыпқа келтіреді және ісіктердің пайда болу ықтималдығын азайтады. Зығыр майы жүрек ауруының қаупін азайтады және қант диабетін емдеу үшін қолданылады. Майлы торт пен шрот малға арналған құнды концентрлі жем болып табылады, құрамындағы ақуызы жағынан ол рапс тортынан еш кем түспейді. Бір килограмм зығыр тортында 1,14 азық бірлігі бар. және 285 г қорытылатын ақуыз.