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Journal of Molecular Biosciences and Engineering

Review Article

UHRF1-DNMT1 Cooperation in DNA Methylation Maintenance: Mechanistic and Oncogenic Insights

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Abstract

In mammalian cells, faithful propagation of DNA methylation patterns during S phase is crucial for epigenetic inheritance. The functional collaboration between DNA methyltransferase 1 (DNMT1) and ubiquitin-like with PHD and RING finger domains 1 (UHRF1) is central to this process. According to structural research, the SRA domain of UHRF1 licenses maintenance methylation by identifying hemi-methylated CpG sites and extruding the methylated cytosine from the duplex via a base-flipping mechanism. Further research revealed that UHRF1 is a multidomain chromatin integrator rather than just a DNA sensor. Its tandem Tudor domain (TTD), plant homeodomain (PHD), ubiquitin-like domain (UBL), and RING finger work together to couple DNA replication, DNMT1 recruitment, and histone state. This pathway is further refined by ubiquitin sensing by the DNMT1 RFTS region and histone H3 ubiquitylation by UHRF1, which help explain how methylation patterns are replicated with high fidelity following replication. Aberrant UHRF1 expression in cancer is frequently linked to poor clinical outcomes, repression of tumor-suppressor networks, and epigenetic instability, particularly in proliferative epithelial malignancies. The idea that UHRF1 and DNMT1 accumulate in replication foci is supported by earlier reports, including findings in HeLa cells. This is consistent with a replication-coupled maintenance machinery functioning in living cancer cells. The structural logic of UHRF1 function, the mechanistic underpinnings of UHRF1-dependent DNMT1 activation, and the mounting evidence that the UHRF1–DNMT1 axis is both an actionable therapeutic vulnerability and a driver of malignant epigenetic maintenance are all covered in this review.

Keywords: UHRF1, DNMT1, DNA methylation, SRA domain, cervical cancer, epigenetic treatment

1. Introduction

Epigenetic modifications are essential for maintaining genome integrity and cellular identity. A key element of epigenetic memory is DNA methylation. The newly synthesized strand is initially unmethylated during DNA replication, while the parental strand retains methyl marks. This results in hemimethylated DNA, which needs to be restored to its fully methylated state. This replication-linked copying process is essential for maintaining cell identity throughout divisions and forms the basis of mitotic epigenetic inheritance. Epigenetic inheritance during the cell cycle requires precise restoration of chromatin modifications following DNA replication, ensuring stable transmission of gene expression patterns through successive cell divisions [1]. Genome-wide epigenomic mapping studies revealed that DNA methylation patterns are highly cell-type specific and must be precisely maintained to preserve cellular identity [2]. The primary maintenance methyltransferase in this context is DNMT1, but its effectiveness and specificity in chromatin are largely dependent on accessory factors rather than just DNA sequence recognition [3].

For maintenance methylation of DNA to be accurate and efficient, additional regulatory factors have evolved that facilitate the recruitment of DNMT1 to newly replicated DNA. Recent studies confirmed that DNA methylation

marks are faithfully transmitted during mitosis through coordinated action of DNMT1 and its regulatory factors at replication sites [4]. Among these factors, the role of ubiquitin-like with PHD and RING finger domains 1 (UHRF1) has gained significant importance in the regulation of DNA methylation in the context of histone modifications and chromatin structures [5], [6]. UHRF1 possesses multiple functional domains through which it simultaneously interacts with hemi-methylated DNA, histones, and chromatin structures associated with DNA replication [7], [8].

UHRF1 was first identified as ICBP90 and found to be a nuclear protein overexpressed in proliferating and cancer cells [9]. Further studies have shown that UHRF1 plays a crucial role in the regulation of epigenetic inheritance and tumorigenesis through the maintenance of aberrant DNA methylation patterns [10]. High levels of UHRF1 in cancer cells, including HeLa cells derived from cervical carcinoma, play a critical role in the silencing of tumor suppressor genes and stabilization of cancer epigenomes [11], [12].

Another important discovery that revealed the mechanism of maintenance methylation by DNMT1 is the base flipping mechanism mediated by the SRA domain of UHRF1 that enables the selective recognition of hemi-methylated DNA [13], [14], [15]. This mechanism, along with chromatin-dependent regulation and ubiquitin signaling, reveals the precise targeting of DNMT1 to replicated DNA.

2. UHRF1 Structure and Cytosine Base Flipping Mechanism

The protein structure of UHRF1 consists of an N-terminal ubiquitin-like domain (UBL), a tandem Tudor domain (TTD), a plant homeodomain (PHD), a SET- and RING-associated domain (SRA), a polybasic region, and a C-terminal RING finger domain. Fig 1. The protein structure of UHRF1 is crucial for the function of the protein because it enables the protein to act as a chromatin sensor that recognizes the signals of DNA methylation, histone modification, and replication [6], [7].

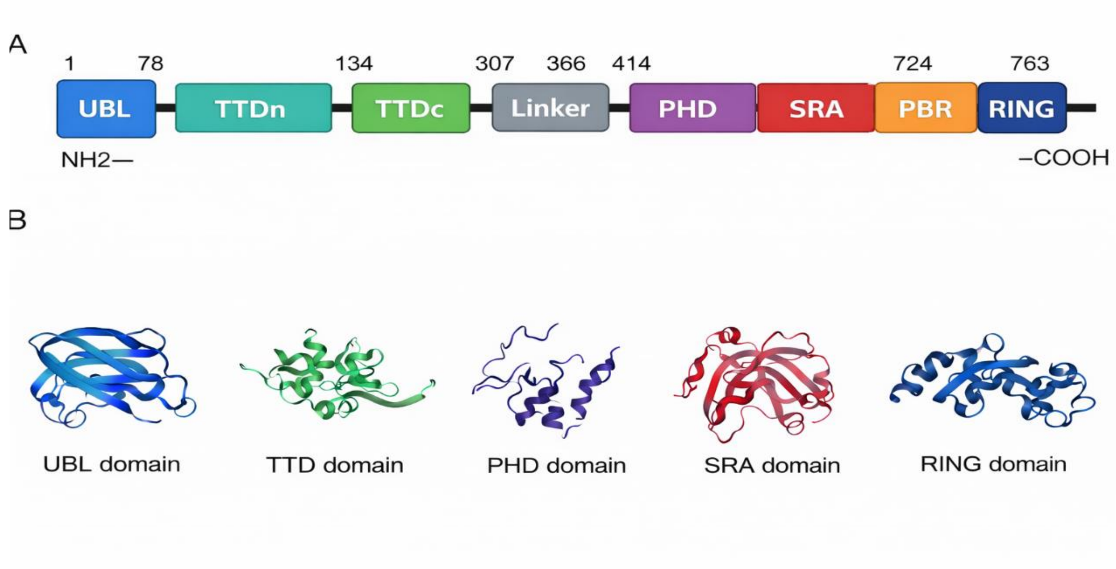

Figure 1. Primary structure of UHRF1 [16].

The spatial structure diagram of UHRF1 domain was obtained from the EMBL-EBI (https://www.ebi.ac.uk/) database (Figure 1). (A) UBL participates in ubiquitination; PHD and TTD are involved in the reading of histone methylation; SRA recognizes hemi-methylated DNA and interacts with DNMT1 and histone deacetylase 1 (HDAC1) and RING has E3 ligase activity. (B) Three-level structure of UHRF1 was illustrated through data obtained from the Protein Data Bank (PDB; http://www.rcsb.org/): UBL has classic α/β folding (PDB; 2FAZ); both TTDn and TTDc of TTD have five strands typical of Tudor family β- folding (PDB; 5×pi); PHD is zinc finger

structure (PDB; 2LGL); on both sides of the SRA are α spiral, the middle is made of β barrel structure formed by folding (PDB: 3BI7); RING has 5 α screw structures (PDB: 3FL2). UHRF1, ubiquitin like with PHD and ring finger domains 1; UBL, N-terminal ubiquitin-like domain; PHD, plant homeodomain; TTD, tandem Tudor domain; SRA, set and ring-associated domain; DNMT1, DNA methyltransferase 1; RING, really interesting new gene domain; PBR, diversity regions.

The interaction between the SRA domain of UHRF1 and DNMT1 contributes not only to maintenance methylation but also to transcriptional regulation of specific genes such as VEGF, highlighting the multifunctional role of UHRF1 in epigenetic control [17]. The SRA domain of UHRF1 plays a crucial role in the maintenance methylation process by recognizing the hemi-methylated CpG sites. The SRA domain recognizes the hemi-methylated CpG sites by flipping the methylated cytosine base out of the helix and into a specific binding pocket [13], [14], [15].

This was confirmed by biophysical experiments that showed the interaction between the SRA domain and DNA was dynamic and sequence-dependent. This supports the view that base flipping is an active rather than passive binding event [18]. Targeting this mechanism has become an attractive strategy for drug discovery. Small molecules that inhibit the base flipping function of UHRF1 have been identified [19], [20].

In addition to the recognition of DNA, the Tudor and PHD domains recognize histone H3 modifications, particularly H3K9 methylation. H3K9 methylation is associated with repressive chromatin [21]. The RING domain of UHRF1 has the capacity to act as an E3 ubiquitin ligase. This allows it to modify histones and establish the appropriate chromatin environment for the recruitment of DNMT1 [22].

Thus, the combination of DNA recognition, histone recognition, and ubiquitination provides the essential role of UHRF1 as the master regulator of epigenetic inheritance.

3. Cooperation Between UHRF1 and DNMT1 in Maintenance Methylation

Maintenance methylation depends on the functional interaction between UHRF1 and DNMT1. Once it binds to hemi-methylated DNA, it recruits DNMT1 to the replication site. This allows the methylation of the newly synthesized DNA strand [23], [8].

One of the crucial mechanisms of the functional interaction between UHRF1 and DNMT1 is the ubiquitination of histone H3 by the RING domain of UHRF1. The monoubiquitination of histone H3 on lysines 18 and 23 provides a binding platform that recruits DNMT1 [22], [24]. Replication factors that also play important roles in the maintenance methylation of DNA include PAF15 and DNA ligase 1 [25], [26].

The activity of UHRF1 is also regulated by conformational changes. Structural studies demonstrated that UHRF1 activity is regulated by intramolecular interactions that control histone binding through allosteric mechanisms, allowing coordinated recognition of chromatin signals [27]. The binding of hemi-methylated DNA or histone ligands induces conformational changes that activate the RING domain of UHRF1 and facilitate the recruitment of DNMT1 [28]. These various modes of regulation ensure that DNMT1 activity is restricted to appropriate genomic locations.

Intramolecular regulation of UHRF1 ensures that its chromatin-binding modules remain inactive until appropriate DNA or histone signals are detected, preventing aberrant methylation activity [29]. Experiments conducted on cancer cells have shown that disruption in the interaction between UHRF1 and DNMT1 results in loss of DNA methylation and thus activation of silenced genes [30], [31]. Association of UHRF1 with methylated H3K9 is essential for proper targeting of DNMT1 to chromatin and ensures accurate maintenance of DNA methylation after replication [32]. These experiments have thus confirmed that UHRF1 is necessary for the maintenance of epigenetic states in proliferating cells.

4. Role of UHRF1-DNMT1 Axis in Cancer and HeLa Cells

Overexpression of UHRF1 has been observed in cancer cells, and it has been associated with hypermethylation of tumor suppressor genes, global methylation, and poor prognosis in cancer patients [33], [34], [35]. UHRF1 thus

maintains methylation patterns in cancer cells, leading to stable silencing of tumor suppressor genes that regulate cell cycle and apoptosis.

In cervical cancer cells, including HeLa cells, UHRF1 is necessary for tumor cell survival. UHRF1 down-regulation in cancer cells results in reactivation of tumor suppressor genes and apoptosis [11], [36], [37]. These experiments have thus shown that cancer cells require methylation maintenance mechanisms to sustain cancer.

The HeLa cell culture model can be used to study the cooperation between UHRF1 and DNMT1. This is because these two proteins are localized in replication foci in S phase, thus showing that there is active methylation machinery in these cells. These findings suggest that the base flipping mechanism and ubiquitin signaling pathway are active in cancer cells, not only in in vitro experiments.

As HeLa cells are derived from cervical carcinoma, they are also a paradigm for understanding how sustained activation of the UHRF1-DNMT1 axis contributes to the maintenance of oncogenic epigenetic states.

5. Therapeutic Perspectives and Conclusion

The key position of UHRF1 as a regulator of maintenance methylation makes it a promising drug target. Several studies have demonstrated that inhibiting UHRF1 expression or activity results in re-expression of tumor suppressor genes and reduced proliferation of tumor cells [36], [38]. Structural studies have identified UHRF1 inhibitors targeting the SRA domain or histone-binding modules, which show that it is possible to pharmacologically target the maintenance methylation machinery [19], [39].

However, it is difficult to discover specific inhibitors of UHRF1 activity as epigenetic enzymes are often pleiotropic. The validation of potential inhibitors is essential to circumvent nonspecific compounds that are common in epigenetic drug screens [40].

In summary, UHRF1 is a multidomain epigenetic integrator that coordinates DNA methylation, histone modifications, and replication-related signals. UHRF1's unique mechanism of action involving a base flipping activity and an ubiquitin-mediated regulation of chromatin is essential for the precise recruitment of DNMT1 to DNA. Because of its central role in maintenance methylation and cancer epigenetics, UHRF1 has been proposed as a promising target for epigenetic therapy. In cancer cells, notably cervical carcinoma cells like HeLa cells, the UHRF1-DNMT1 axis is disrupted to maintain oncogenic epigenetic states. The understanding of UHRF1-DNMT1 cooperativity at a molecular level could provide new opportunities for epigenetic therapy.

Author Contributions

The author contributed to the conceptualization and methodology of the study, prepared, reviewed, and edited the manuscript.

Conflict of Interest

The author declares no competing financial or personal interests.

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Abbreviations

Cytosine–Phosphate–Guanine Dinucleotide (CpG), Deoxyribonucleic Acid (DNA), DNA Methyltransferase 1 (DNMT1), Ubiquitin Ligase Enzyme (E3), Histone H3 Lysine 9 (H3K9), Histone Deacetylase 1 (HDAC1), Human Cervical Carcinoma Cell Line (HeLa), DNA Ligase 1 (LIG1), PCNA-Associated Factor 15 (PAF15), Polybasic Region (PBR), Protein Data Bank (PDB), Plant Homeodomain (PHD), Really Interesting New Gene Domain (RING), Ribonucleic Acid (RNA), SET and RING-Associated Domain (SRA), Tandem Tudor Domain (TTD), Ubiquitin-like Domain (UBL), Ubiquitin-like with PHD and RING Finger Domains 1 (UHRF1), Ubiquitin-specific Protease (USP7).

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Journal of Molecular Biosciences and Engineering

Review Article

Stem Cells: Basic Concepts, Methods, Challenges, and Prospects

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Abstract

Stem cells are undifferentiated cells that can self-renew and transform into different cell types. These cells, created during the embryonic period, are found in the body after birth, mainly in places such as bone marrow, fat tissue, and blood. Stem cells play an important role in the regeneration of damaged tissues and are used for therapeutic purposes, especially mesenchymal stem cells. The healing potential of these cells is widely used in the treatment of chronic wounds and orthopedic problems. Unlike muscle cells, blood cells, or nerve cells, which do not reproduce normally, stem cells can reproduce many times. When a stem cell divides, it can become two daughter cells: 1) both can be daughter cells; 2) one stem cell, another different cell; 3) both are different cells. There are two main types of stem cells: embryonic stem cells and developmental stem cells. Stem cell therapy plays an important role in the treatment of many diseases, such as heart diseases, nervous system diseases, and various types of cancer. The regenerative capacity of the root system works by two main mechanisms: asymmetric cell division and stochastic differentiation. In asymmetric division, a stem cell produces a cell similar to itself and a cell that will differentiate. In stochastic differentiation, a stem cell divides into two different daughter cells and creates a new stem cell.

Keywords: stem cell, bone marrow, adipose tissue, cord blood, asymmetric cell, stochastic differentiation

1. Introduction

The ability of stem cells to continuously renew themselves allows them to maintain their populations. These cells can initiate the formation and regeneration of various tissues and organs through differentiation (Figure 1) [1]. In this regard, the article describes the history of development, basic concepts, and classifications of stem cell research and application in medicine [2], [3].

Human pluripotent stem cells (hPSCs) principally consist of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs). Whereas induced pluripotent stem cells are produced by reprogramming differentiated somatic cells, embryonic stem cells come from the inner cell mass of the early embryo. Ectoderm, mesoderm, and endoderm are the three germ layers from which pluripotent stem cells can differentiate [4].

However, adult stem cells are multipotent and or unipotent, and they produce only the cell types appropriate for the specific environment they are living in. The regenerative abilities of stem cells create significant opportunities in cell-based therapies for the repair and replacement of damaged tissues and organs.

Stem cells formation: Embryonic stem cells are formed during the first 4 weeks after fertilization and can differentiate into all cell types. They exist in the blastocyst stage of embryonic development. An important feature of embryonic stem cells is their ability to differentiate into different cell types. However, due to some ethical issues, there are restrictions on the use of medicine. The main application of embryonic stem cells in medicine is due to their significant potential in the regeneration of damaged tissues [5], [6], [7], [8].

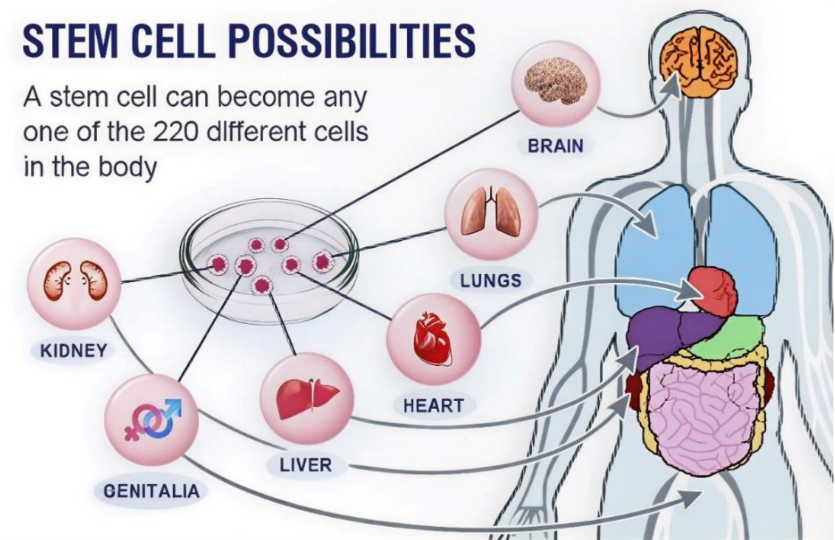

Figure 1. Differentiation of stem cells [1].

Past: The concept of "stem cells" first began with the work of Alexander A. Maksimov in 1909. His early research focused on their development and their main role in disease.

Present: Currently, stem cells are widely used in cancer treatment, regenerative medicine, and pharmacological testing. The induced pluripotent stem cell (iPSC) method allows the development of personalized therapies without raising ethical concerns.

Future: Future applications of innovations such as bioprinting and advanced 3D culture will create new opportunities in tissue engineering and organ replacement. However, challenges remain regarding clinical safety and efficacy [9].

Key stages in stem cell development:

1959 - The first animal (rabbit) was produced by IVF.
1968 - Edwards and Bavister fertilize the first human egg in vitro.
1978 - The first IVF baby is born in England.
1981 - Evans and Kaufman obtain mouse embryonic stem cells.
1996 - Rhesus monkey embryonic stem cells are obtained.
1998 - Thomson and colleagues obtained the first human embryonic stem cell.
2000 - Human embryonic stem cells are shown to be pluripotent.
2001 - United States President Bush approves a limited budget for stem cell research and only allows research using embryos left over from in vitro fertilization [1].
2004 - South Korean scientists clone 30 human embryos and bring them to the blastocyst stage, but only 1 of these embryos can be used to obtain stem cells [1].

2. Ethical Concerns Surrounding Embryonic Stem Cell Research

The main ethical issue in embryonic stem cell research concerns the destruction of human embryos. The moral status of the embryo and whether it is considered a potential human life raises serious questions. Many critics argue that the destruction of embryos is tantamount to the termination of a human life. However, its supporters point out that significant medical advances are possible as a result of such research.

These include the requirement for written consent from donors for embryos resulting from in vitro fertilization (IVF), as well as concerns about the exploitation of vulnerable populations. In addition, discussions about creating embryos solely for research purposes and providing financial compensation to oocyte (egg) donors can raise ethical dilemmas [10].

3. Cultivation and Expansion of Embryonic Stem Cells

Several technologies are used in the cultivation and application of embryonic stem cells:

Cell Culture: Cells obtained from blastocysts are maintained in a specialized nutrient medium for 3-12 months without undergoing differentiation.

Cryopreservation: Stem cells are frozen at low temperatures for long-term storage while preserving their biological characteristics.

Stable Cell Lines: Stem cells derived from human embryos are used to establish stable cell lines capable of indefinite division [11].

Modern technologies include:

Induced Pluripotent Stem Cells (iPSCs): This technology reprograms mature cells into embryonic-like pluripotent cells, reducing ethical concerns and enabling personalized medical applications.

Tissue Engineering: Bioprinting and three-dimensional (3D) culture systems are employed to guide stem cells into forming specific tissues.

Stem Cell Transplantation: The therapeutic use of autologous (self-derived) and donor-derived stem cells is increasingly expanding in the treatment of various diseases [12].

The application of stem cell technology has brought revolutionary advances in the field of regenerative medicine.

Most advanced and effective approaches:

iPSCs: Provide pluripotent cells without the need to destroy embryos, allowing broader clinical and research applications.

Bioprinting: 3D printing techniques allow the formation of tissue-like structures from stem cells, promising breakthroughs in organ repair and replacement.

Tissue Engineering: Enables the restoration of damaged tissues using stem-cell-based biological scaffolds and growth systems [13], [14].

Biotechnological products such as amino acids, hormones, enzymes, and vaccines are widely used to stimulate cell growth and produce biopharmaceuticals. Advances in genetics, molecular biology, microbiology, and enzymology have increased the efficiency of these processes [15].

4. Required Environment for Embryonic Stem Cell Expansion

To prevent embryonic stem cells from differentiating, a special nutrient-rich culture medium is required. The culture medium is regularly supplemented with fibroblast feeder layers, allowing these stem cells to remain undifferentiated for 3-12 months.

Embryonic stem cells are isolated from the inner cell mass of the blastocyst using special enzymatic methods. They can be kept alive for a long time by freezing at extremely low temperatures.

Environmental requirements:

Food composition: The environment should contain some vitamins, amino acids, mineral salts, and sugars that are essential for growth and metabolism.

Oxygen levels: The correct oxygen concentration is important. Thus, a CO_2 concentration of 5-10% and an O_2 concentration of about 21% are considered optimal.

pH: A pH between 7.2 and 7.4 is considered ideal for stem cell culture.

Temperature: The optimal temperature for active cell division and growth of embryonic stem cells is 37°C.

By providing the above conditions, it is possible to store embryonic stem cells for a long time while maintaining their number.

5. Types of Stem Cells

Stem cells are cells that can self-renew and differentiate into other cell types (Table 1). There are three main types:

Totipotent Stem Cells: These cells can develop into all tissues and organs, including both the body (embryonic tissues) and extraembryonic structures such as the placenta. They exist at the earliest stages of embryonic development [16].

Pluripotent Stem Cells: Found from the blastocyst stage of the embryo, these cells can differentiate into almost all cell types of the body, but they cannot form extraembryonic tissues such as the placenta. Embryonic stem cells (ESCs) belong to this group.

Multipotent Stem Cells: These are adult stem cells that can differentiate into a limited range of cell types within a specific tissue or organ. For example, hematopoietic stem cells in bone marrow can produce various types of blood cells. (Figure 2) [17], [18].

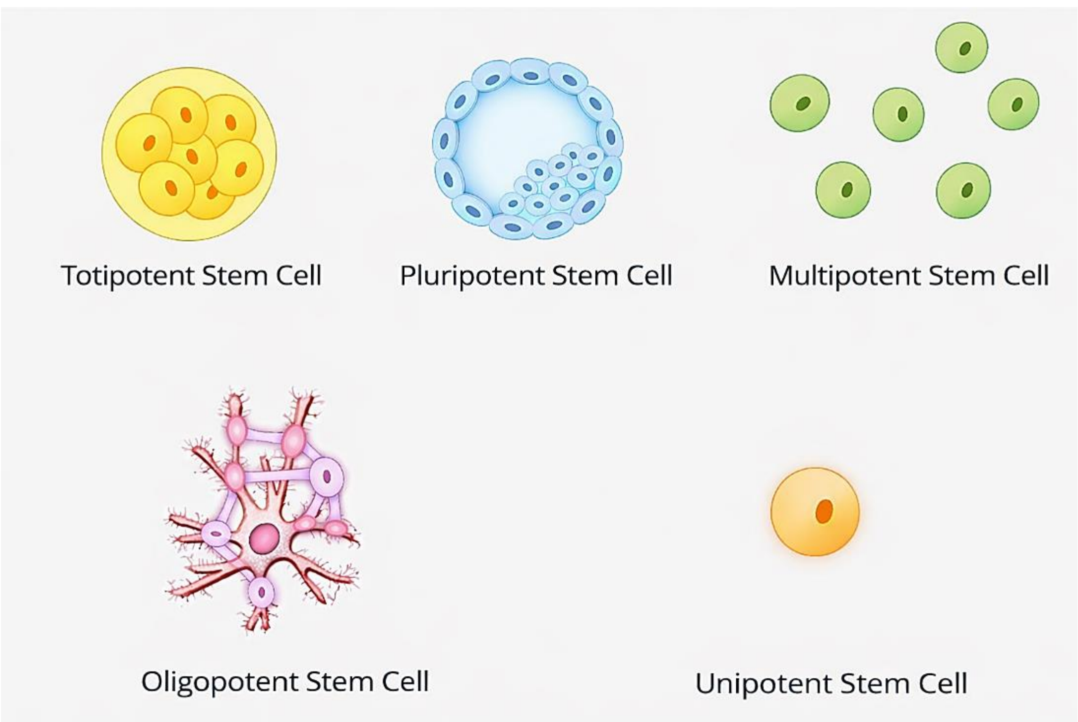

Figure 2. Types of stem cells.

5.1. Totipotent Stem Cells

Totipotent cells are cells that can differentiate into all cell types, including both embryonic tissues (all tissues and organs of the body) and extraembryonic tissues such as the placenta and amniotic fluid. They arise at the very earliest stage of development, beginning from the zygote, and retain their totipotency during the first few cell divisions. Key characteristics of totipotent cells include:

Ability to divide extensively and self-renew.
Capacity to regenerate all tissue types, including support structures needed for embryonic development.
Full synthesis of mRNAs and proteins is required for complete embryonic development.

5.2. Pluripotent Stem Cells

Pluripotent cells are mainly found in the epiblast of early mammalian embryos, particularly during the blastocyst stage. These cells have the potential to differentiate into the three primary germ layers: Ectoderm, Mesoderm, Endoderm, as well as germ (reproductive) cells.

After implantation, the epiblast maintains pluripotency but transitions into a "primed" state in preparation for gastrulation, where lineage specification begins. This pluripotent state is transient and usually lasts only until gastrulation occurs (e.g., in mice, approximately 6.5-9.5 days after fertilization).

5.3. Induced Pluripotent Stem Cells (iPSCs)

Pluripotent stem cells can also be generated from adult tissues using iPSC technology, which reprograms somatic cells (often skin or blood cells) back to a pluripotent state. Steps include:

Cell Collection: Adult cells are obtained through skin biopsy or blood sampling.

Genetic Reprogramming: Key transcription factors (e.g., Oct4, Sox2, Klf4, c-Myc) are introduced using viral or non-viral delivery methods.

Cell Culture: Reprogrammed cells are grown in conditions that maintain pluripotency.

This method avoids ethical issues associated with embryonic stem cell use and enables patient- specific regenerative therapies [10].

Table 1. Difference between totipotent and pluripotent cells.

Feature	Totipotent Cells	Pluripotent Cells
Can form body cells	Yes	Yes
Can form a placenta and extraembryonic tissues	Yes	No
Stage in development	Zygote & early divisions	Inner cell mass of the blastocyst

Pluripotent stem cells are valuable in regenerative medicine**,** especially for repairing damaged tissues and treating diseases such as degenerative disorders and certain cancers.

5.4. Multipotent Stem Cells

Multipotent cells are stem cells present at later developmental stages that can differentiate into a limited range of specialized cell types (Table 2). For example:

"Hematopoietic stem cells" in bone marrow can form all types of blood cells [19], [20].
"Mesenchymal stem cells (MSCs)" can differentiate into bone, cartilage, and muscle cells.

These cells play a key role in repairing damaged tissues in the adult body and are more limited in developmental potential than pluripotent cells [21], [22], [23]. Functional differentiation assays are also used to verify their ability to form specialized cell types.

Table 2. Multipotent stem cells are identified using specific cell surface markers.

Stem Cell Type	Common Markers	Methods Used
Hematopoietic stem cells	CD34, CD45	Flow cytometry, immunocytochemistry
Mesenchymal stem cells	CD73, CD90, CD105	Flow cytometry

Multipotent stem cells are used for:

Tissue repair (e.g., heart tissue regeneration, spinal cord injury treatment).
Immunomodulation (particularly MSCs in autoimmune disease therapy).
Clinical trials for diseases such as myocardial infarction and ALS.

Importantly, they carry a lower risk of tumor formation compared to pluripotent cells.

6. Adult (Somatic) Stem Cells in Aging

In adults, somatic stem cells repair and replace damaged tissues. However, their numbers gradually decrease with age:

In newborns, ~1 in 10,000 cells is a stem cell
In elderly individuals: ~1 in 1,000,000 cells is a stem cell

This decrease causes slower wound healing and reduces regenerative capacity. The following processes can be performed with stem cell-based therapies in older patients: Improve tissue repair, increase functional recovery, and enhance overall quality of life.

The therapeutic effect of stem cells is usually observed within 3-6 months and can last for 6-12 months, depending on the age and health status of the person.

7. Cell Division in Stem Cells

Stem cells are divided into two ways: asymmetric and symmetric.

During asymmetric division, one stem cell and one differentiated (specialized) cell are formed from one stem cell. This allows stem cells to both self-renew and create specific cell types.

During symmetric division, two identical stem cells are produced. In this way, only the number of stem cells increases, but it does not contribute to functional diversity.

Both symmetric and asymmetric divisions are very important for tissue regeneration and development. That is, the main importance of symmetric division is to support tissue regeneration by increasing the number of stem cells. Producing identical copies of stem cells ensures the preservation of the stem cell population, which is very important for the regeneration of damaged tissues. Symmetrical division of stem cells plays an important role in therapeutic applications such as wound healing and tissue regeneration.

The role of asymmetric division of stem cells is to ensure their differentiation into different specialized cell types, which are important for the development and regeneration of the organism. In this way, stem cells maintain their population and at the same time generate new cells with specific functions (Table 3). They allow the formation of various cell types necessary for tissue function. Thus, they contribute to the overall health of the person and the repair of damaged areas.

Table 3. Differences between symmetric and asymmetric stem cell division.

Feature	Symmetric Division	Asymmetric Division
Cell Outcome	Produces two identical stem cells	Produces one stem cell and one differentiated cell
Functional Diversity	Cells share the same function	Cells have different functions
Self-Renewal	Increases the number of stem cells	Maintains self-renewal while supporting differentiation
Role in Development	Promotes tissue growth	Essential for tissue regeneration

8. Diseases Treated with Stem Cells

Stem cells are used to treat the following diseases:

- Cancer (leukemias, lymphomas, brain tumors)
- Bone and cartilage disorders
- Immune deficiency conditions
- Bone marrow diseases
- Hereditary blood disorders
- Metabolic disorders

In addition, stem cell therapy is showing promising results in ongoing research for diseases such as breast cancer, heart disease, and neurological disorders.

The main role of stem cells in treatment is to repair and regenerate damaged tissues. Mesenchymal stem cells are commonly obtained from fat, bone, and cartilage tissues and have the potential to repair damaged tissues in diseases such as arthritis. When stem cells are injected into damaged areas, they stimulate the regeneration process, reduce inflammation, and help form new blood vessels. This method has shown promising outcomes in the treatment of many diseases, including cancer, diabetes, and heart disease (Figure 3) [24].

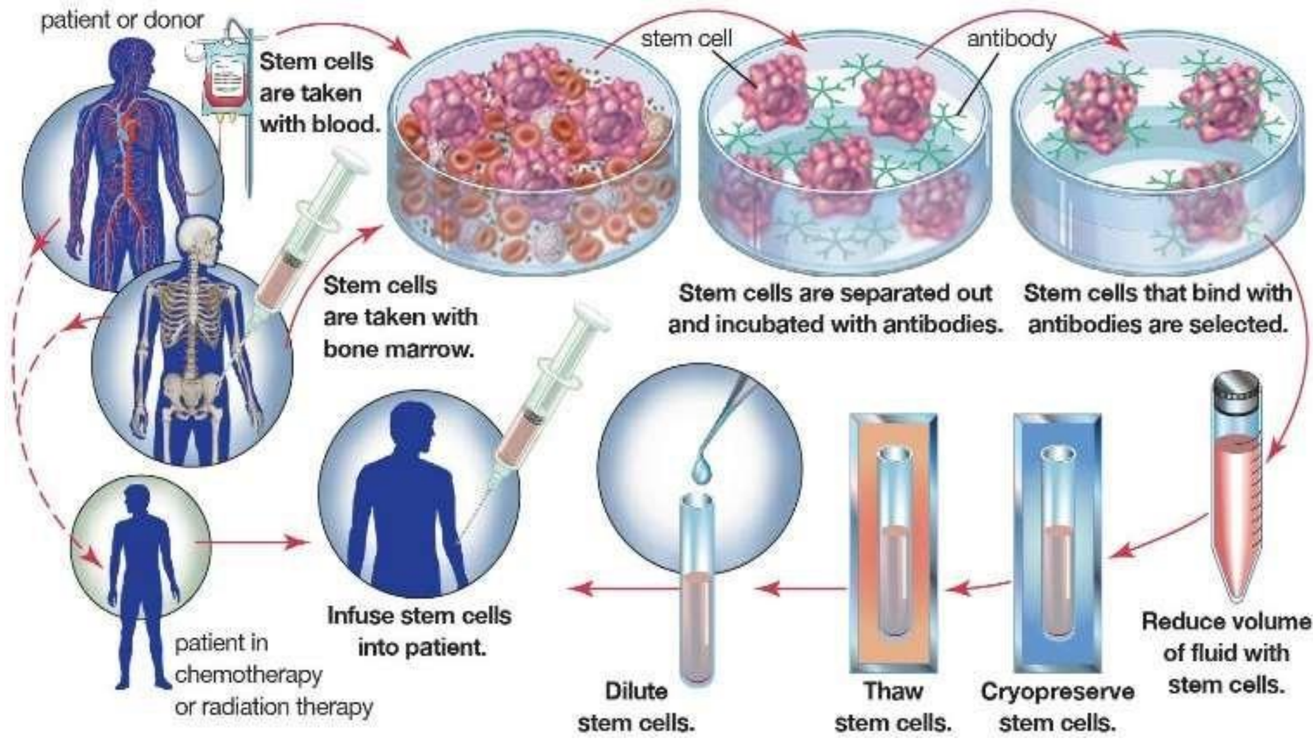

Figure 3. Clinical application of stem cells [24].

The reserve of stem cells depends on age. In newborns, about 1 in every 10,000 cells is a stem cell, but by the age of 65, this ratio drops to about 1 in 1 million. As the body ages, the number of stem cells decreases, making tissue repair more difficult. Stem cells can differentiate into needed cell types and have self-renewal capacity.

Stem cell therapy is commonly used in the treatment of cancer, particularly blood cancer and lymphoma. The therapy usually begins with chemotherapy to destroy cancer cells, followed by the transplantation of healthy stem cells. These stem cells help restore the immune system and play a role in repairing damaged tissues, for example, in heart failure and other conditions. However, there are also several risks associated with stem cell treatment, including cancer.

8.1. Cancer

Stem cell therapy is an effective approach to treating cancer, especially blood cancers and lymphomas. Treatment begins with high-dose chemotherapy, followed by a transplant of healthy stem cells that help restore the immune system. Stem cell therapy accelerates healing by allowing damaged tissues to regenerate. The disadvantage of stem cells is that they can interact with cancer cells and support their spread and growth. Therefore, stem cell therapy should be carried out under very strict medical supervision.

8.2. Bone and Cartilage Diseases

Stem cell therapy is particularly effective in the treatment of cartilage damage. Since they can self-renew and differentiate into different types of tissue, they can stimulate the regeneration of cartilage tissue. Stem cells, especially those derived from adipose tissue, are widely used in the treatment of bone and cartilage damage. Many studies have shown that this therapy accelerates joint healing and reduces pain. The speed and duration of cartilage damage treatment usually vary between 3 and 6 months, depending on the severity of the injury, the effectiveness of the treatment, and the age of the patient. The therapy may be applied in several sessions.

8.3. Immune Deficiency

There are several mechanisms for strengthening the immune system with stem cells:

Tissue repair: Helps repair damaged tissues and supports immune function.

Inflammation reduction: Helps reduce inflammatory processes in the body and increases immune efficiency.

Production of new cells: Strengthens the body's defense system and can transform into various immune cells.

These treatment methods are often used in autoimmune diseases and other immune deficiencies.

Methods used in the treatment of immunodeficiency:

Hematopoietic stem cell transplantation: This method restores the immune system in diseases such as leukemia and lymphoma.

Mesenchymal stem cells: Reduce inflammation and support tissue repair in autoimmune diseases.

Intravenous Infusion and Local Injection: Increases the recovery of damaged tissues.

8.4. Bone Marrow Diseases

Bone marrow diseases are caused by abnormalities in the development of stem cells. Stem cells can differentiate into white blood cells, red blood cells, and platelets. In diseases such as leukemia, aplastic anemia, and myeloproliferative disorders, the bone marrow fails to produce healthy blood cells. Stem Cell therapy helps repair damaged tissue and stimulates the production of normal blood cells.

8.5. Hereditary Blood Disorders

Stem cells also play an important role in the treatment of hereditary blood diseases. Since they can differentiate into several cell types, they can restore blood cell production and support regeneration. This treatment method is very useful in cases where the number of stem cells naturally decreases with age.

9. Neurological Diseases

Stem cell therapy is a promising approach in the treatment of neurological diseases. In diseases such as Alzheimer's, Parkinson's disease, and spinal cord injuries, stem cells can support the regeneration of damaged neurons and reduce their functional impairment. From the perspective of regenerative medicine, stem cells enhance the body's ability to repair itself and support the healing of damaged tissues. Although the effectiveness of stem cells depends on the individual patient's condition, they offer new hope in the treatment of neurological

diseases [25].

9.1. Parkinson's Disease

Stem cell therapy has shown quite positive results in the treatment of Parkinson's disease. The study found that stem cells can help improve motor function and replace dopamine-producing neurons in some patients. However, as the process is still in its development stage, its effectiveness will vary depending on the specific characteristics of each case. Thus, stem cell therapy is considered a promising method for the treatment of Parkinson's disease. However, further long-term observation and clinical studies are needed to determine its full effectiveness and safety [26].

9.2. Alzheimer's Disease

The main potential role of stem cells in the treatment of Alzheimer's disease is due to their neuroprotective and regenerative properties. Stem cells are thought to help reduce inflammation in the body, repair damaged neurons, and potentially reduce the accumulation of amyloid-beta protein. Researchers also note that exosomes derived from stem cells may stimulate nerve regeneration and improve memory mechanisms. In general, this therapy is still in the clinical research phase and requires further studies to fully confirm its effectiveness. As a result of the research, the following benefits are suggested:

Neuroprotective effects: Protect nerve tissue in the brain by reducing neuronal damage.

Reduction of inflammation: Slowing disease progression.

Potential for reducing amyloid-beta accumulation: Alleviating symptoms of the disease.

Improving memory and learning: Possible through signaling molecules derived from stem cells.

These possibilities of stem cell therapy make it a promising future approach to Alzheimer's disease [26].

10. Errors and Risks in Stem Cell Therapy

Because stem cells do not always function properly in the body, they can sometimes cause complications, including abnormal cell growth or tumor formation. If the body's immune system identifies the transplanted stem cells as foreign, it may immediately destroy them or cause harmful inflammatory reactions. Therefore, autologous stem cell therapy is considered safer than donor-based transplantation. Possible complications include:

Immune Rejection: Transplanted stem cells may be recognized as foreign and destroyed.

Incorrect Differentiation: Stem cells may transform into unintended cell types, damaging tissues.

Infection Risk: Extraction and transplantation procedures carry a risk of infection.

Additional Major Risks:

Tumor Formation (Oncogenic Risk): Poorly controlled differentiation may lead to malignant cell growth.

Immune Reactions: Transplanted cells may trigger strong immune responses.

Graft Failure: Transplanted cells may fail to engraft and produce new blood cells (especially in bone marrow transplantation).

Graft-versus-Host Disease (GvHD): Donor immune cells may attack the recipient's tissues.

Increased Infection Vulnerability: Immune suppression after transplantation increases.

Due to the risks mentioned, stem cells need to be used under highly professional clinical supervision [27].

11. Conclusion

The discovery and application of stem cells is considered one of the greatest advances in the history of medicine. They are widely used in many fields and continue to be widely used. One of the most notable aspects is their ability to slow down the aging process, and one of their greatest clinical importance is their role in the treatment of chronic and degenerative diseases. They are also of particular importance in transplantation therapies and regenerative medicine.

Stem cell therapy has shown significant results in the repair of heart, joint, liver, and nerve tissue injuries. They may have therapeutic benefits in wound healing, tissue regeneration, and diseases such as diabetic wounds and osteoarthritis.

Many studies also show potential fertility-enhancing effects in some cases. However, clinical trials are ongoing to determine safety with respect to tumorigenesis and other conditions. With the development of science and technology, it is expected that more and more obstacles to treatment will be removed. Stem cell approaches are currently being investigated for the treatment of neurological diseases, and their effectiveness is expected to increase in the future. According to some scientists, stem cells could allow for advances in human longevity, the regeneration of all tissues, and even adaptation to new environments, including life beyond Earth.

Author Contributions

Both authors contributed substantially to the study and approved the submitted version.

Conflict of Interest

The authors declare no conflicts of interest.

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Abbreviations

Embryonic Stem Cells (ESCs), Human Pluripotent Stem Cells (hPSCs), Induced Pluripotent Stem Cells (iPSCs), In Vitro Fertilization (IVF), Three-Dimensional (3D), Carbon Dioxide (CO_2), Mesenchymal Stem Cells (MSCs), Amyotrophic Lateral Sclerosis (ALS), Graft-versus-Host Disease (GvHD).

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Review Article

Conceptual Basis of Turner Syndrome

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Abstract

Turner Syndrome (TS) is a relatively common chromosomal disorder affecting females. It is characterized by the partial or complete absence of one of the X chromosomes, resulting in a wide range of physical, developmental, and medical difficulties. TS has been the subject of extensive research and clinical studies, providing valuable insights into the genetic and physiological basis of female development. This article aims to provide a comprehensive overview of the conceptual basis of Turner Syndrome, its genetic origins, clinical manifestations, diagnostic criteria, and current therapeutic approaches.

Keywords: Turner syndrome, symptoms, X chromosome, diagnosis, treatment

1. Introduction

Turner Syndrome (TS) is a chromosomal condition that affects only females and is caused by the partial or complete absence of one of the two X chromosomes. Henry Turner described the syndrome in 1938, and it is named after him. The manifestation of the condition can vary, but common features include short stature, specific physical features, and dysgenesis of the genitals leading to infertility.

Turner syndrome is a hereditary disease that primarily impacts females. It is caused by the absence of one or all of the X chromosomes, the chromosomes that determine a person's sex. As a result, girls with Turner syndrome have distinct physical and intellectual characteristics. These include [1]:

- Short stature
- Neck creases
- Low hairline on the back of the neck
- Broad chest
- Narrow nose

Turner syndrome can also cause some intellectual and developmental problems, such as learning disabilities, delayed speech development, and attention and memory problems. However, with appropriate care and intervention, many people with Turner syndrome live full and productive lives. The disease was first described as hereditary in 1925 by the Soviet endocrinologist N.A. Shereshevsky. He then proved that the disease was caused by underdevelopment of the gonads and anterior pituitary gland and was associated with congenital defects. Shereshevsky-Turner syndrome was described in more detail by Dr. Henry Turner in 1938. Dr. Turner was an endocrinologist and medical geneticist working in the United States. In his seminal article, he described the clinical features of a group of girls with short stature, short necks with wing-like curls, and other physical features characteristic of this disorder. He also noted the presence of ovarian dysgenesis and infertility, which are hallmarks of Turner syndrome. Since its initial description, the syndrome has been further characterized and is now widely

recognized as a distinct genetic disorder. Today, the diagnosis of Turner syndrome is based on a combination of physical examination, genetic testing, and medical history.

2. X Chromosome Abnormalities in Turner Syndrome

Turner syndrome is caused by the absence of one or all of the X chromosomes (Figure 1) [3]. Generally, females possess two X chromosomes, whereas males possess one X and one Y chromosome. In Turner syndrome, females are missing either the entire X chromosome (45, X) or part of one X chromosome (45, X/46, XX mosaicism).

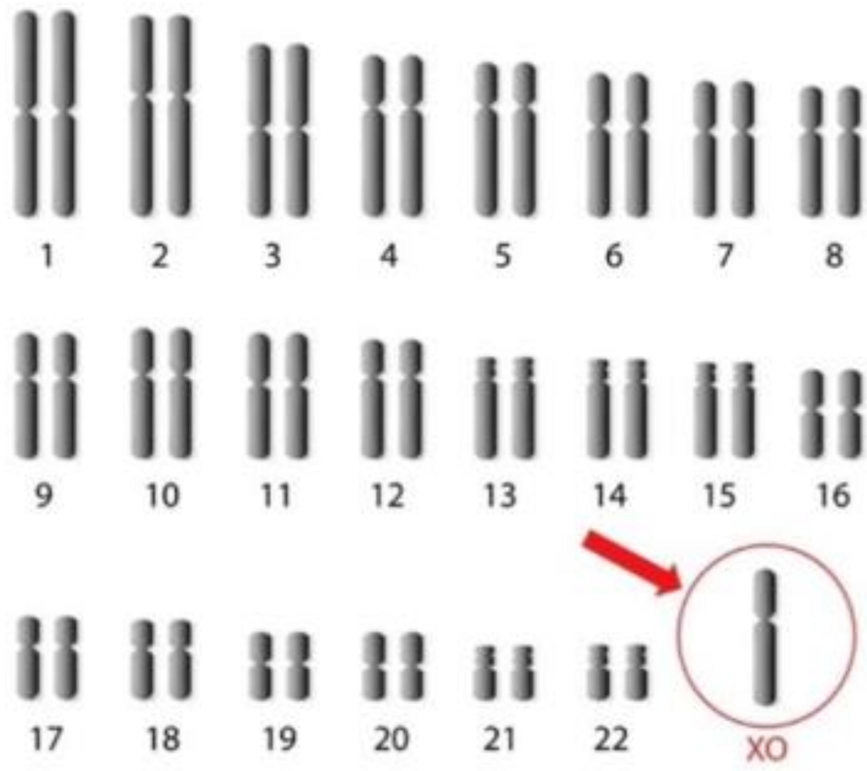

Figure 1. Chromosomal abnormalities in individuals with Turner syndrome [2], [3].

There are several genetic variants of Turner syndrome. These are the following:

Monosomy X (45, X): This is a condition in which a woman is missing one of her two X chromosomes. This can occur as a result of a random error during cell division in a developing egg or fetus.

Structural anomalies: This is a condition in which part of one of a woman's X chromosomes is missing or altered.

Mosaicism: This is a condition where some cells have two typical X chromosomes, while others have only one X chromosome or a structurally altered X chromosome [4].

The absence or alteration of the X chromosome can cause the characteristic physical and intellectual characteristics of Turner syndrome, as well as several other health problems. It is necessary to note that Turner syndrome is not caused by anything the mother does during pregnancy or how she raises the child. It is a spontaneous genetic event.

3. Symptoms of Turner Syndrome

Some of the most common physiological symptoms of Turner syndrome include (Figure 2) [3]:

Short stature: This is the most obvious and well-known characteristic of Turner syndrome. Girls with Turner syndrome are significantly shorter than their peers, and their growth hormone production stops at an early age.

Ovarian Dysfunction: Turner syndrome is associated with ovarian dysgenesis, which is the failure of the ovaries to develop normally. This leads to the absence of menstruation and infertility.

Heart defects: Some people with Turner syndrome may have structural heart abnormalities such as a bicuspid aortic valve, coarctation of the aorta, or patent ductus arteriosus.

Skeletal problems: Girls with Turner syndrome may have spinal abnormalities such as scoliosis, as well as joint problems such as dislocation.

Kidney problems: Some people with Turner syndrome may have structural kidney abnormalities, such as a horseshoe kidney, which is a fusion of two kidneys.

Learning disabilities: Some people with Turner syndrome may have difficulties with math and spatial skills, as well as mental deficits such as attention and memory problems.

Hearing problems: Some people with Turner syndrome may experience hearing loss, especially in the high-frequency range [5].

It is necessary to note that not all people with Turner syndrome will experience all of these symptoms, and the severity of symptoms can vary greatly. In addition, many girls with Turner syndrome can return to normal lives with proper care and treatment.

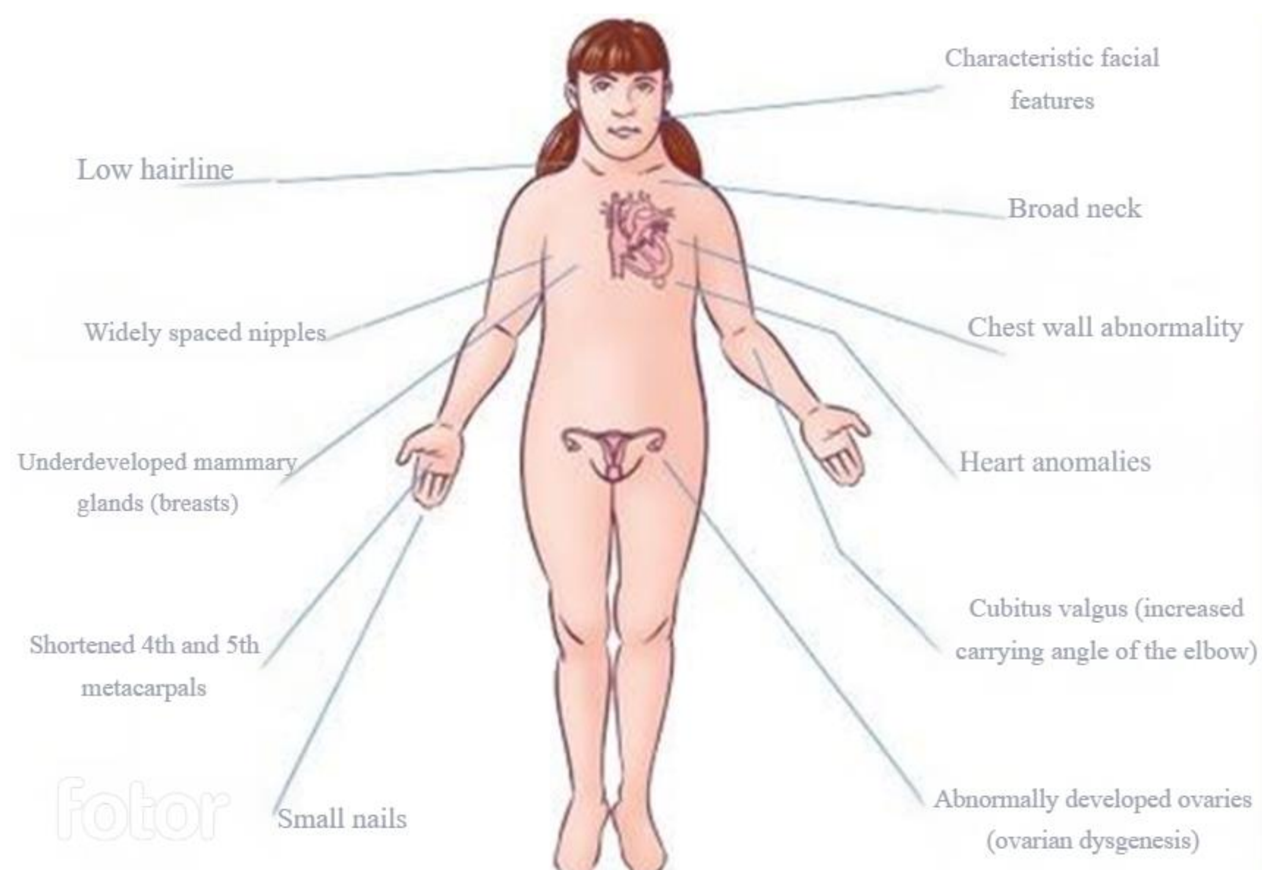

Figure 2. Appearance of a person with Turner syndrome [3].

4. Diagnosis of Turner Syndrome

Turner syndrome is usually diagnosed through a combination of physical examination, genetic testing, and medical history. Some diagnostic tools that may be used to diagnose Turner syndrome include:

Physical examination: During the examination, the doctor detects the characteristic physical signs of Turner syndrome, such as short stature, a broad chest, a short neck with wing-like folds, a low hairline at the back of the neck, narrow hips, and a high palate.

Blood tests: Blood tests can be used to analyze levels of hormones such as follicle-stimulating hormones (FSH), which are essential for ovarian function. Elevated FSH levels may indicate that the ovaries are not functioning properly, which is a characteristic feature of Turner syndrome.

Chromosome analysis: Chromosome analysis, also known as karyotyping or cytogenetic testing, is a laboratory test used to determine the number and structure of chromosomes. In Turner syndrome, a woman may have only one X chromosome (45, X) or she may have two X chromosomes, but one of them has a structural change (45, X/46, XX mosaicism).

Ultrasound: Ultrasound can be used to assess the condition of internal organs such as the heart, kidneys, and ovaries. In some cases, ultrasounds can detect structural abnormalities characteristic of Turner syndrome.

It should be noted that the diagnosis of Turner syndrome is not always clear; several tests may be required to clarify the diagnosis, but the final diagnosis is made based on the results of cytogenetic research (karyotype analysis).
Prenatal tests performed during pregnancy may reveal the presence of Turner syndrome (Figure 3) [6].

Ultrasound: A first-trimester screening test that assesses the fluid accumulation behind the fetus's neck. An aberrant reading signifies a chromosomal abnormality. This diagnostic test is conducted between 10 and 12 weeks of gestation for women with an abnormal first-trimester screening result. A minor specimen of the placenta, referred to as the chorionic villus, is examined for chromosomal anomalies [7].

Amniocentesis is conducted between 15 and 18 weeks of gestation. A sample of amniotic fluid, which surrounds the fetus, is collected and examined for aberrant protein levels that may signify particular diseases.

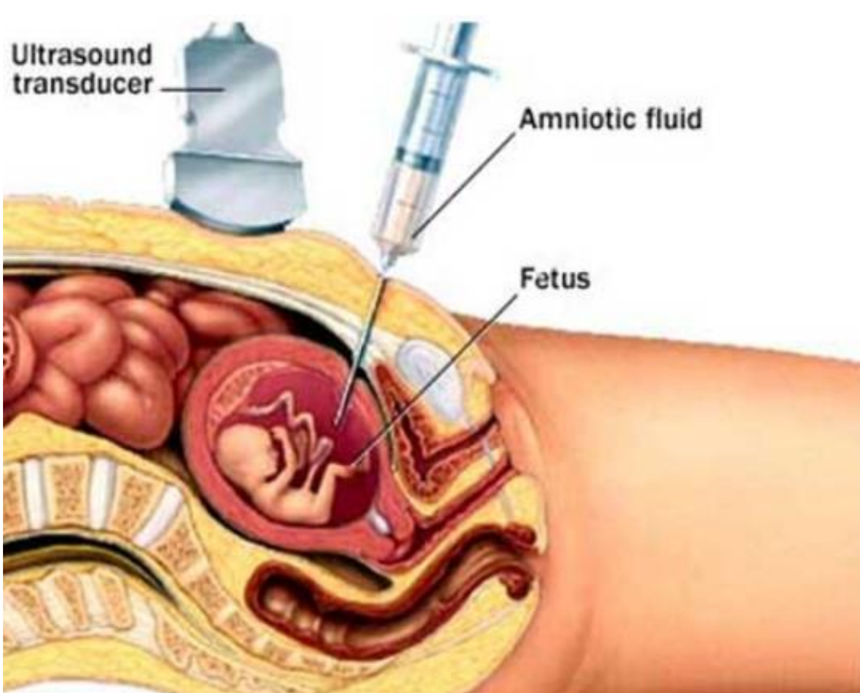

Figure 3. Tests to detect disease during pregnancy [6].

5. Treatment Strategies in Turner Syndrome

Turner syndrome is a chronic disorder without a cure; nevertheless, recent advancements in genetics and current treatment choices have significantly improved the lives of affected girls and women. Females with Turner syndrome may experience additional medical issues that require ongoing treatment and management throughout their lives. Growth hormone supplementation represents conventional therapy for height enhancement. The increase in height at the end of treatment is dependent upon various circumstances, including the age at which therapy begins, the length of treatment, and the administered hormone dosage [8]. Supplementing with growth hormones should begin at age 4 or as soon as the disease is recognized, whichever happens first. Research indicates that after 3-7 years of treatment, patients may achieve an increase in height of roughly 8-10 cm. No adverse consequences have been recorded. The majority of individuals necessitate ovarian hormone therapy, specifically estrogen, a female sex hormone. This can begin between the ages of 12 and 15 to initiate puberty and sustain normal female endocrine function. This is also crucial to the formation of additional sexual behaviors. Hormone replacement treatment (HRT) is crucial as it mitigates the risks linked to ovarian failure, particularly osteoporosis and cardiovascular disease. Hormone levels should be regularly monitored [8].

New efforts in assisted reproduction have created the possibility of pregnancy in these patients. Pregnancy rates of over 50% have been reported in patients with spontaneous menstruation. However, these patients exhibit a higher susceptibility to miscarriage and chromosomal anomalies. Twins are more typical. In a separate team, where patients possess completely striated ovaries, fertilization can be achieved via donated eggs. Heart valve problems appear in 30% of females with the condition. Surgical intervention or regular consultations with a cardiologist, accompanied by routine ultrasonography or echocardiography. Cardiac imaging assessments should be performed [9]. Hypertension is induced by the constriction of the aorta. Narrowing can be repaired surgically, or hypertension can be managed with pharmacological interventions. Hearing aids can be used to treat hearing issues brought on by childhood middle ear infections. Estrogen therapy can be used to treat osteoporosis, or bone thinning. Thyroid function tests should be used to monitor thyroid diseases. It is necessary to control metabolic diseases like diabetes and obesity. Ultrasound is necessary on a regular basis for kidney abnormalities. Regular exercise and a healthy lifestyle can be beneficial. Although the condition has no known treatment, females who suffer can live normal lives, but they typically require the care of multiple doctors.

6. Conclusion

When TS is diagnosed, the family should be provided with professional support from a medical geneticist, pediatric endocrinologist, or physician specializing in TS. TS can be diagnosed prenatally by ultrasound (USG) demonstrating fetal edema or a cystic hygroma of the neck. Ultrasonographically, left heart defect, renal anomalies, growth retardation, or relatively short limbs may indicate TS.

Author Contributions

Laman A. Huseynova conducted the literature search and drafted the manuscript. Saltanat A. Aghayeva supervised the study, provided critical guidance on content and structure, and reviewed the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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Abbreviations

Turner Syndrome (TS), Follicle-Stimulating Hormone (FSH), Hormone Replacement Treatment (HRT), Ultrasonography (USG).

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Review Article

Molecular Mechanisms Causing SMA Pathology

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Abstract

Disorders in genes and chromosomes lead to various genetic diseases. These diseases can be inherited from parents to future generations or arise from mutations that form spontaneously in genetic material. Researching genetic diseases is extremely important because it helps to understand the mechanisms that cause the disease and to provide effective interventions. As a result, diagnostic methods are being improved and targeted treatments and preventive measures are being developed. One of the crucial genetic diseases is Spinal Muscular Atrophy (SMA). SMA has a significant impact on quality of life, causing severe physical disabilities and, in some cases, life-threatening complications. The study of SMA also serves as a model for understanding other neurodegenerative and genetic diseases.

Keywords: spinal muscular atrophy, SMN1 and SMN2 genes, SMN protein, splicing mechanism, alternative splicing

1. Introduction

Spinal muscular atrophy (SMA) is a devastating genetic disorder that primarily affects motor neurons in the spinal cord. This neuromuscular disease results in progressive muscle wasting and muscle weakness. Spinal muscular atrophy is considered one of the most common inherited causes of child mortality worldwide. The disease is caused by mutations in the survival motor neuron (SMN) genes, namely SMN1 and SMN2. Mutations in the survival motor neuron (SMN) genes, namely SMN1 and SMN2, are the main cause of the disease. Knowledge about the processes that cause SMA has increased significantly in recent years, providing insight into the complex interplay of cellular processes that underlie the pathogenesis of the disease. This article examines the roles of the SMN1 and SMN2 genes, RNA splicing processes, and molecular genetic mechanisms involved in the pathogenesis of SMA [1], [2].

2. General Information About SMA

Mutations or deletions in the SMN1 (survival motor neuron) gene, located on chromosome 5q13, are the main cause of the genetic disease spinal muscular atrophy (SMA). Motor neurons are nerve cells in the spinal cord that allow impulses to be sent from the spinal cord to the muscles. The deficiency of the SMN protein, which is essential for the structure and function of motor neurons, is caused by mutations in the SMN gene. Insufficient and progressive loss of SMN protein results in motor neuron (synaptic) dysfunction and degeneration, resulting in muscle atrophy and weakness [1], [2]. Approximately one in 10,000 newborns worldwide is affected by SMA. SMA is thought to be one of the most common hereditary causes of neonatal death. SMA has an autosomal recessive inheritance pattern. Accordingly, the disease can only be manifested in an individual who inherits two copies of the mutant SMN1 gene, one from each parent. Carriers have one mutant and one normal copy of the

SMN1 gene. Studies suggest that about 1 in 40 to 60 people carry the defective SMN1 gene. Carriers can pass the defective gene on to their offspring, but they do not show symptoms of the disease. The symptoms of SMA vary depending on the type and severity of the disease. There are 5 types of SMA (Type 0, I, II, III, IV) [3], [4], [5].

The disease is usually caused by a homozygous deletion. Either exons 7 and 8 are deleted together, or exon 7 alone is deleted. In the remaining cases, small intragenic and de nova mutations have been identified [5], [6]. Both SMN1 and SMN2 genes are located on chromosome 5 in the region q11-13 [1], [2]. The SMN1 and SMN2 genes, which have a similar structure, are composed of 10 exons. Although the SMN gene was previously reported to consist of nine exons, recent studies have shown that it consists of ten exons. Exon 6b was discovered by exon fission of an Alu element in intron 6 [7]. Although the SMN1 and SMN2 genes are 99% identical (homology), there are 5 nucleotides that differentiate them. There are 3 differences in introns 6 and 7 in the non-protein-coding regions, and 2 differences in exons 7 and 8 in the coding regions. Mutations in the SMA gene cause a decrease in SMN protein levels. The severity of the disease phenotype is related to the copy number of the paralogous gene, SMN2, which produces a less stable form of the SMN protein. The milder symptoms of the disease are associated with a higher SMN2 copy number. The copy number of the SMN2 gene differs between the types of the disease, with fewer in Type 0 and more in Type 4 [8]. However, low levels of methylation of the SMN2 gene are associated with milder symptoms of the disease, as the disease may develop differently due to epigenetic processes that methylate DNA and silence the SMN2 gene. Studies have found that patients with different types of SMA have different levels of methylation at positions -296 and -290 in two CpG islands of SMN2 [9]. A hallmark of SMA pathology is aberrant splicing of SMN2 pre-mRNA transcripts. The C-to-T transition of exon 7 damages a potential exonic splicing enhancer (ESE). This is the main molecular abnormality responsible for SMA. The silent nucleotide exchange results in the replacement of a C in the SMN1 gene (TTC → TTT at position 280) with a T in the SMN2 gene. This region surrounding exon 7 is important because it causes a change in the resulting mRNA. In most SMN2 transcripts, the loss of SMN1 is not fully compensated for by a single nucleotide difference that causes exon 7 skipping. In alternative splicing, deletion of exon 7 in the SMN2 gene results in the production of a truncated and unstable SMN protein isoform. This isoform lacks critical functional domains and is termed SMNΔ7. This impairs its ability to participate in snRNP assembly and other cellular processes essential for the survival of motor neurons [10], [11], [12].

3. Factors Affecting the Regulation of Splicing

In general, several factors influence the regulation of SMN gene splicing: a combination of regulatory proteins, cis-acting elements, and trans-acting factors. To influence splicing, several proteins, including RNA-binding proteins and splicing factors, interact with specific sequences present in the pre-mRNA from SMN. For example, the SMN protein controls the splicing of its own transcripts by forming complexes with other splicing factors, such as gemin proteins. The two most common forms of RBP are heterogeneous ribonucleoprotein (hRNP) and serine/arginine-rich (SR) proteins. When RNA-binding proteins bind to the ISS or ESS, exon removal is promoted, and the formation of the spliceosome complex is inhibited. The same gene transcript can produce different end products depending on the tissue to which the RBPs bind. The different splicing mechanisms of these proteins result in different combinations of exons and introns [12]. SMN genes have certain sequences called cis-acting elements that act as binding sites for regulatory protein binding. These cis-acting components, which promote or prevent the inclusion of exon 7 in SMN2, include exon splicing enhancers (ESEs) and exon splicing silencers (ESSs). SMN splicing can also be influenced by RNA or proteins synthesized by other genes. These are trans-acting factors. For example, various physiological signals or environmental influences can affect the activity or expression level of splicing regulatory proteins.

The transition in the protein-coding region of the SMN2 gene results in the skipping of exon 7. The Tudor domain, an important component of the SMN protein that is involved in binding to various RNA and protein molecules, is encoded by exon 7. In the absence of exon 7 in SMNΔ7, the function of the Tudor domain is impaired. This, in turn, disrupts the protein's interaction with other molecular proteins. This loss of function is

associated with the reduced stability and activity of SMNΔ7 when compared to the full-length SMN protein produced by SMN1.

Deletion of exon 7 of the SMN2 gene occurs through alternative splicing. This results in the production of a less functional SMN protein. Some splicing factors influence the skipping of exon 7 [13], [14]. These include positive and negative regulatory splicing factors. For example, SRSF1 (serine/arginine-rich splicing factor 1) and Tra2B (transforming protein 2 homolog β) are positive regulatory factors. Both splicing factors bind to the enhancer regions of exon 7, called SE1 and SE2. In this case, exon 7 is not skipped. Conversely, exon 7 is spliced out when negative regulatory factors bind to SE1. Examples of these include heterogeneous nuclear ribonucleoprotein A1 (hnRNP A1) and the src-associated substrate in mitosis 68. Negative regulation may also occur through the binding of hnRNP A1 to the SE2 and N1 regions [15], [16], [17]. SMN1 expression is dominated by positive splicing regulation. Cooperative binding of hnRNP G and SRSF9 is enabled by TRA2B, further enhancing the beneficial effects of exon 7 recognition. The U1 and U2 snRNPs are therefore recruited to exon boundaries, and inclusion of this exon depends on recognition by this snRNP. The U1 and U2 snRNPs are attracted to exon boundaries for these reasons, and inclusion of this exon depends on recognition by this snRNP. SMN2 transcripts contain a C to U substitution in the SE1 region, which allows the negative regulator hnRNP A1 to bind to this site. SAM68 can bind to this site and exert a similarly damaging effect. SAM68 can bind to this site and exert a similarly damaging effect. It is known that there are two additional hnRNP A1 regions in the SE2 region and the intronic silencing element ISS-N1 that cause exon 7 exclusion. There are negative effector proteins that reduce the recognition of the exon by U1 and U2 snRNPs, leading to the exclusion of exon 7. Inclusion of exon 7 in both SMN1 and SMN2 transcripts is facilitated by the binding of hnRNP M to a region in SE2 that overlaps with the TRA2B binding site (Figure1) [8].

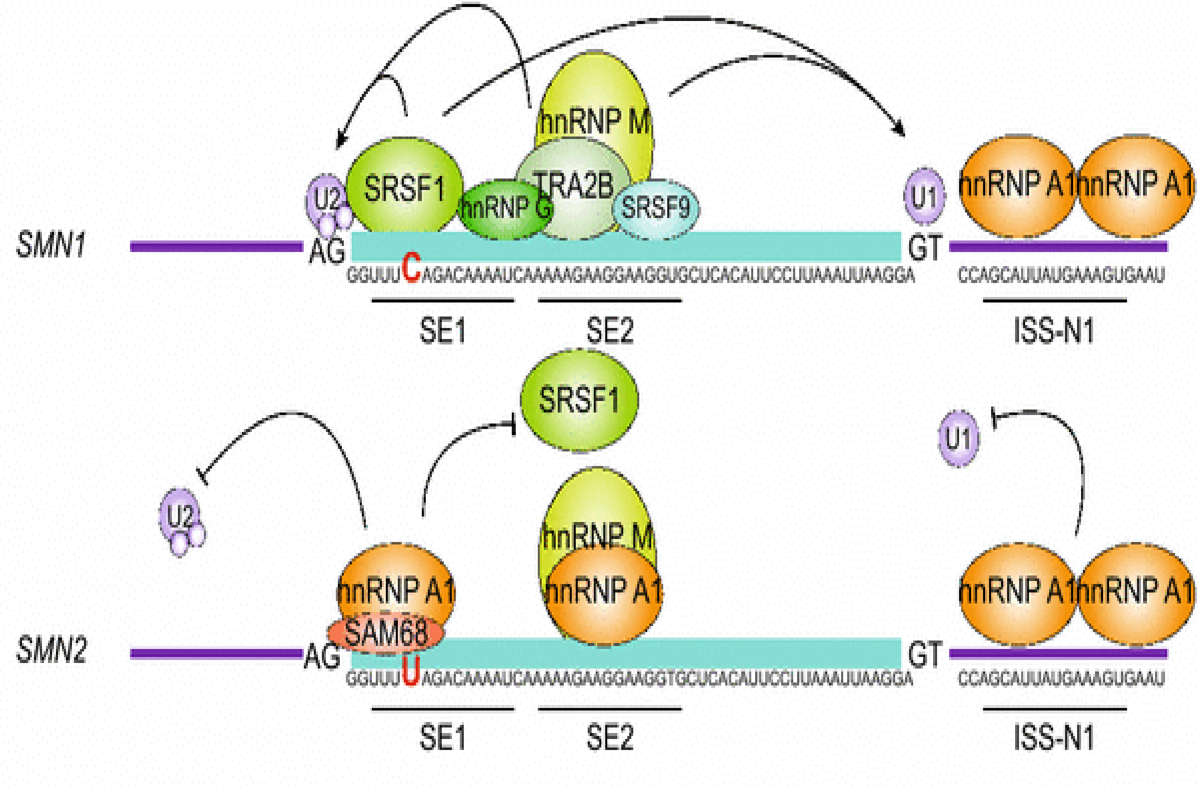

Figure 1. SMN1 and SMN2 exon 7 splicing regulators [8].

The SMN protein plays a significant role in snRNP formation and mRNA transport, which are essential for the proper functioning of motor neurons. Its structural domains allow it to interact with various proteins and RNA,

which contribute to necessary biological processes. SMN is essential for the functioning of motor neurons, as deficiencies in the protein cause severe neurodegenerative defects. Deficiency of this protein leads to degeneration and loss of motor neurons, resulting in muscle weakness. It is the SMN protein that plays a crucial role in the assembly of snRNPs, which are essential components of the spliceosome. The process of pre-mRNA splicing, a crucial step in mRNA development, is carried out by the spliceosome. It affects physiological processes such as transcription and RNA metabolism by forming multiprotein complexes. The SMN protein Gemin 2-8 and Unrip combine to form the SMN-Gemin complex, which plays an important role in the biogenesis of snRNPs. Smn proteins bind to snRNPs in a complex to form small nuclear ribonucleoprotein particles (snRNPs). Without the SMN protein, snRNPs cannot assemble, and motor axon functions are impaired. This complex facilitates the transport of snRNPs from the cytoplasm to the nucleus and their assembly. The SMN protein plays a crucial role in the transport and translation of mRNAs in axons in motor neurons. SMN's function in axonal transport, particularly the movement of β-actin mRNA from motor neurons to axonal growth cones, has been studied. Reduced levels of SMN protein are associated with impaired β-actin transport to axon terminals via microtubules [18], [19], [20]. The maintenance of motor neurons and muscle function depends on the function and plasticity of synapses. They play a role in the appropriate activity of lower motor neurons in the anterior horn of the spinal cord and the bulbar nuclei of the cranial nerves. SMN protein is found in the nucleus and cytoplasm. In the cytoplasm, SMN is found in granules that are involved in the transport of mRNA and ribonucleoprotein complexes along axons. In the nucleus, SMN is assembled into subnuclear structures called "gems". These are considered to be sites of snRNP biogenesis and recycling. The amount of protein varies between different organs and tissues of the body, such as the kidney, liver, heart, skeletal muscle, fibroblasts, and lymphocytes [21]. SMN protein co-localizes with various SMN complex components in axons, and most SMN granules do not contain SMN proteins located in the axonal compartment. Neurochondrin, a neuronal-specific protein, co-localizes with snRNPs and participates in cytoplasmic localization. SMN protein also has the ability to bind to the -COP component of the COPI vesicle. In primary cortical neurons, neurite outgrowth in NSC-34 cells is reduced in the absence of -COP. As a result, SMN localization and accumulation are altered. SMN and -COP are required simultaneously for proper neurite production [22]. The SMN protein is approximately 38 kDa in size and consists of 294 amino acids [23], [24]. Structural analysis of the SMN protein suggests that it consists of several major domains with specific functions. Exons 2a-2b contain a potential nucleic acid binding site, located at the N-terminal end. This domain binds to Gemin2, another protein in the SMN complex. This interaction is essential for the stability and function of the SMN complex. The Tudor domain binds to symmetrically dimethylated arginine (sDMA) residues on target proteins and facilitates interactions with various RNA-binding proteins. This domain is located in exon 3. The domain located in exon 5 is a proline-rich region, located in the central part of the protein and involved in protein-protein interactions. The Y/G box is a glycine-rich region towards the C-terminus of the protein involved in RNA binding and oligomerization and is located in exon 7. The 3'-untranslated region is localized in the region of exon 8 [25], [26].

Recent therapeutic advances in SMA have focused on restoring functional SMN protein levels to improve disease symptoms and clinical outcomes. Numerous therapeutic approaches have been developed to promote the inclusion of exon 7 in SMN2 transcripts and thereby increase the production of full-length SMN protein. These strategies include antisense oligonucleotides (ASOs) designed to mask exon splice sites, small molecules that modulate splicing factors, and gene editing techniques to correct underlying mutations [27], [28]. In particular, ASOs and small molecules act by modulating the splicing of the SMN2 gene. Antisense oligonucleotides, which are short chains of synthetic nucleic acids, prevent the skipping of exon 7 in the SMN2 mRNA transcript. The first drug approved by the FDA was nusinersen, which contains ASOs. This drug, which only aims to restore SMN expression in the central nervous system, also has side effects such as headaches, back pain, vomiting, constipation, lower respiratory tract infections, etc. Other drugs that act as splicing modifiers are small molecules such as Risdiplam, which act as an ASO and increase SMN protein expression. Despite some side effects, it improves motor function by targeting both the central and peripheral nervous systems [29], [30].

4. Conclusion

The molecular mechanisms underlying the pathology of spinal muscular atrophy (SMA) are complex and multifaceted. It involves a cascade of genetic, molecular, and cellular events, primarily resulting from a deficiency of the SMN protein. Understanding splicing defects and other dysfunctions is clarifying how SMN deficiency causes muscle atrophy, leading to the development of promising therapeutic approaches aimed at restoring SMN protein levels.

Author Contributions

A.I. Dadashova wrote the manuscript under the supervision and review of M.A. Abbasov. Both authors reviewed and approved the final manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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Abbreviations

Spinal Muscular Atrophy (SMA), Survival Motor Neuron (SMN), Deoxyribonucleic Acid (DNA), Ribonucleic Acid (RNA), Messenger Ribonucleic Acid (mRNA), Small Nuclear Ribonucleoprotein (snRNP), RNA-Binding Protein (RBP), Heterogeneous Ribonucleoprotein (hRNP), Heterogeneous Nuclear Ribonucleoprotein (hnRNP), Exonic Splicing Enhancers (ESE), Exonic Splicing Silencers (ESS), Intronic Splicing Silencer (ISS), Serine/Arginine-Rich (SR), Serine/Arginine-Rich Splicing Factor 1 (SRSF1), Transforming protein 2 homolog β (Tra2B), Src-Sssociated in Mitosis, 68 kDa (SAM68), Symmetrically Dimethylated Arginine (sDMA), Coat Protein Complex I (COPI), Antisense Oligonucleotides (ASOs), Food and Drug Administration (FDA).

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Review Article

Role of BRCA1 and BRCA2 Mutations in the Molecular Genetic Mechanisms of Ovarian Cancer

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Abstract

Ovarian cancer is one of the most lethal oncological diseases among women, and hereditary factors play a crucial role in its pathogenesis. In this regard, the BRCA1 and BRCA2 genes are of particular importance as key tumor suppressor genes involved in the repair of DNA double-strand breaks through homologous recombination. Pathogenic mutations in these genes lead to disruptions in genome stability, the accumulation of DNA damage, and uncontrolled cell proliferation. As a result, the risk of developing ovarian cancer increases significantly. BRCA1 and BRCA2 gene mutations can be both hereditary (germinal) and somatic, and the spectrum of these mutations encompasses point mutations, insertion-deletion changes, and loss of large genomic segments. At the molecular-genetic level, these changes weaken DNA repair mechanisms and activate alternative, error-prone repair pathways. Recent studies have shown that ovarian cancer in BRCA mutation carriers has a different biological behavior and response to treatment; in particular, there is a high sensitivity to PARP inhibitors. For this reason, studying the molecular-genetic roles and mutation mechanisms of the BRCA1 and BRCA2 genes is of significant scientific and clinical importance for personalized diagnostics, risk assessment, and the development of targeted therapies.

Keywords: ovarian cancer, BRCA1 and BRCA2 genes, PARP inhibitor, DNA repair, gene mutation, targeted therapy

1. Introduction

Ovarian cancer is considered one of the most severe and complex oncological diseases of the female reproductive system and is characterized by high mortality rates. One of the main reasons for the danger of this disease is that clinical symptoms are non-specific or completely absent in the early stages. As a result, a large proportion of patients are diagnosed at late stages, which limits treatment options and reduces the likelihood of survival. Modern scientific research on the etiology and pathogenesis of ovarian cancer shows that not only environmental and hormonal factors, but also genetic and molecular mechanisms play a crucial role in the development of the disease [1].

Genetic predisposition is considered one of the most significant risk factors for the development of ovarian cancer. Mutations in the BRCA1 and BRCA2 genes, particularly within the framework of hereditary breast and ovarian cancer syndrome, necessarily increase the risk of developing the disease. These genes are tumor suppressor genes that perform necessary functions in maintaining the structural integrity of DNA in the cell, repairing damaged DNA sites, and regulating the cell cycle. Loss of their functional activity leads to disruption of genome stability and the creation of favorable conditions for malignant transformation [2].

In terms of molecular-genetic mechanisms, the BRCA1 and BRCA2 genes are mainly involved in the repair of DNA double-strand breaks through homologous recombination. This mechanism is considered one of the most reliable DNA repair pathways for the cell. However, when mutations occur in the mentioned genes, this

mechanism becomes ineffective, and the cell resorts to alternative, but more error-prone, repair pathways. Consequently, the mutation load increases, chromosomal abnormalities arise, and the process of tumor cell formation accelerates. In this regard, BRCA gene mutations are central to the molecular pathogenesis of ovarian cancer.

Mutations observed in the BRCA1 and BRCA2 genes can be germline (hereditary) and somatic in origin. Germline mutations are passed down from generation to generation, leading to an increase in familial ovarian cancer cases. Somatic mutations, on the other hand, arise later in tumor tissue and directly affect the course of the disease and response to treatment. The breadth of the mutation spectrum, including point mutations, insertions, and deletions, as well as large genomic rearrangements, suggests that functional loss of these genes can occur by various mechanisms [3].

In recent years, advances in molecular genetics and genomics have led to fundamental changes in the diagnostic and treatment strategies of ovarian cancer. Detection of BRCA mutations is of great importance for early screening of at-risk individuals, planning preventive measures, and implementing personalized treatment approaches. The introduction of targeted drugs, particularly PARP inhibitors, into clinical practice has led to improved treatment outcomes in BRCA mutation carriers. These drugs selectively target tumor cells by exploiting DNA repair deficiencies and have minimal effect on healthy cells.

Thus, studying the molecular-genetic role and mutation mechanisms of BRCA1 and BRCA2 genes in ovarian cancer is of significant scientific and practical importance not only in terms of understanding the biological basis of the disease, but also in clinical decision-making, assessing prognosis, and selecting effective treatment strategies. Systematic research on this topic will facilitate the development of oncogenetic approaches, the application of personalized medicine, and the formation of new perspectives in the fight against ovarian cancer.

2. Molecular-Genetic Mechanisms of BRCA1 and BRCA2 in Ovarian Cancer

Analysis of the molecular-genetic basis of ovarian cancer demonstrates that disturbances in DNA repair mechanisms play a crucial role in the development of the disease. In this context, the BRCA1 and BRCA2 genes are of particular importance as key tumor suppressor genes that maintain genome stability. Their functional loss leads to an increase in the accumulation of genetic damage in the cell, chromosomal instability, and, ultimately, malignant transformation.

In a healthy cell, the BRCA1 and BRCA2 genes ensure the high-fidelity repair of DNA double-strand breaks through homologous recombination. While BRCA1 is involved in damage recognition and recruitment of repair complexes, BRCA2 plays a role primarily in directing the RAD51 protein to the site of DNA damage. This interaction maintains the genetic integrity of the cell and ensures the normal continuation of the cell cycle [2].

A sister chromatid is one of two genetically identical copies of the same chromosome, formed by DNA replication before cell division. These two chromatids are joined together by the centromere and are separated and distributed to daughter cells during the processes of mitosis and meiosis. Mutations in the BRCA1 and BRCA2 genes cause loss of gene function through various molecular mechanisms. The most common types of mutations include:

- *Point mutations (missense and nonsense mutations)*
- *Insertions and deletions, resulting in frameshifting*
- *Large genomic deletions and duplications*

As a result of these mutations, the proteins synthesized are either completely dysfunctional or unable to participate in intracellular repair processes (Figure 1) [4]. In the end, the homologous recombination mechanism breaks down, and the cell resorts to inaccurate, error-prone alternative DNA repair pathways (e.g., non-homologous joining) [5].

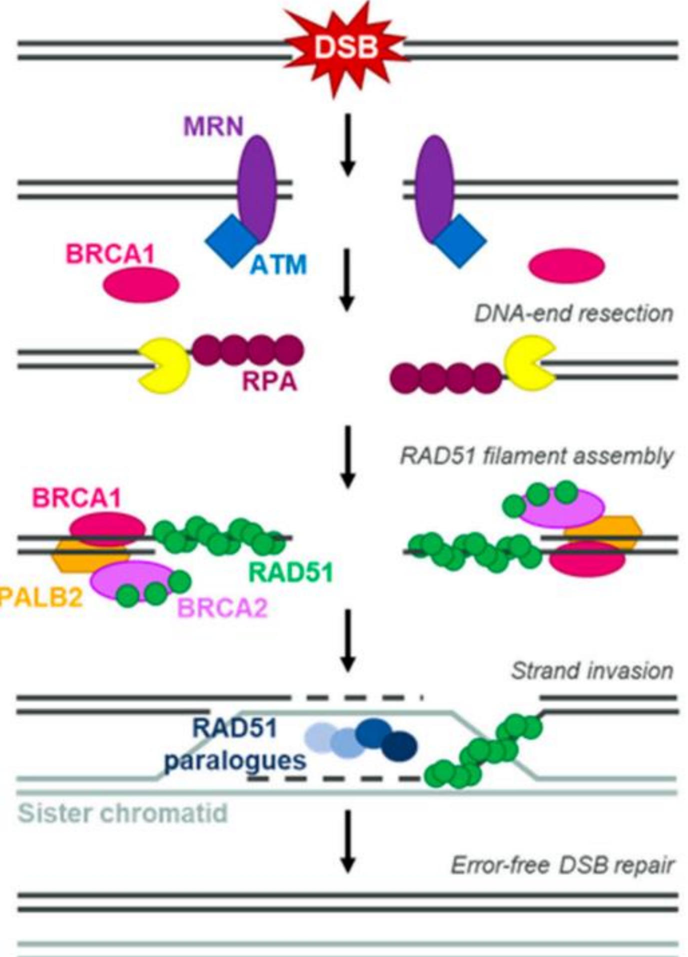


Figure 1. The error-free repair mechanism of DNA double-strand breaks via homologous recombination involving the BRCA1 and BRCA2 genes [4].

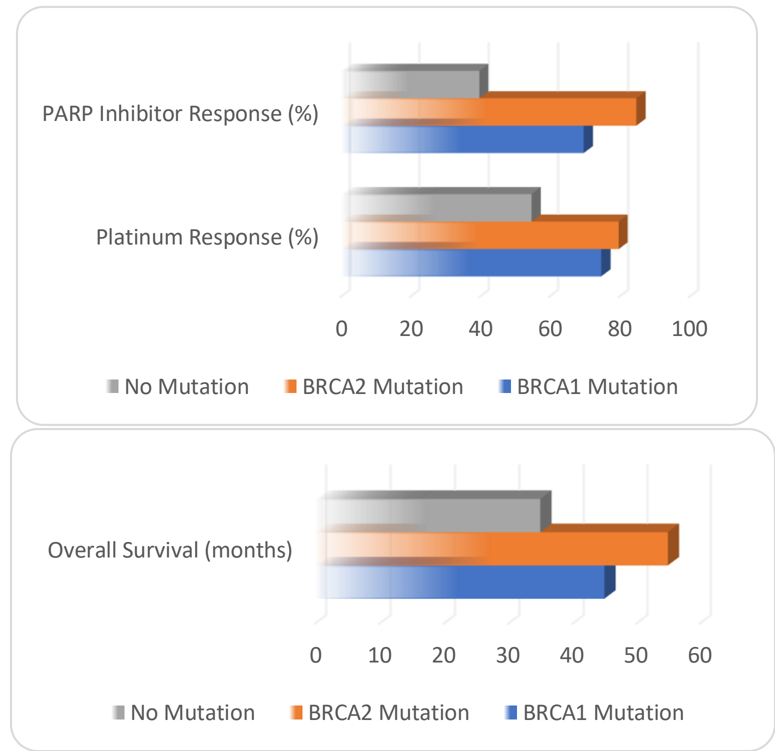
Table 1. Types of mutations in the BRCA1 and BRCA2 genes and their molecular-genetic and clinical consequences [6].

Mutation Type	Molecular Properties	Effect on BRCA Protein	Results at the Cellular Level	Relationship with Ovarian Cancer
Point mutations (missense)	Amino acid substitution resulting from a change in a single nucleotide	Partial impairment of protein function	Decreased efficiency of homologous recombination	Moderate risk increase
Nonsense mutations	Premature stop codon generation	Abbreviated and non-functional protein synthesis	Complete disruption of the DNA repair mechanism	High-risk, aggressive tumors
Insertions and deletions (frameshift)	Violation of the reading frame	Complete functional loss	Increased genomic instability	Strong link with hereditary ovarian cancer
Large genomic deletions	Loss of a large portion of the gene	Failure to synthesize the BRCA protein	Activation of error-prone DNA repair pathways	Early onset, high risk
Somatic mutations	Occurs only in tumor tissue	Local BRCA loss of function	Selective vulnerability in tumor cells	Hypersensitivity to PARP inhibitors
Germinal mutations	It is hereditary and present in all cells	Systemic BRCA deficiency	Chronic genomic instability	Familial risk of ovarian cancer

In Table 1, the main types of mutations observed in the BRCA1 and BRCA2 genes, their molecular-genetic characteristics, and the functional changes they cause at the cellular level are systematically presented [6]. The mutations shown here disrupt the structural and functional integrity of BRCA proteins through various mechanisms, reducing the efficiency of DNA repair through homologous recombination. Consequently, genomic instability occurs in cells, and favorable conditions are created for malignant transformation.

BRCA mutations in ovarian cancer are divided into two main groups based on their origin: germline and somatic mutations. Germline mutations are present in all cells and are considered the main genetic cause of hereditary breast-ovarian cancer syndrome. Carriers of such mutations have a significantly increased risk of ovarian cancer, and the disease can occur at an earlier age. Somatic mutations, on the other hand, form only in tumor tissue and are not hereditary. However, from a clinical perspective, these mutations are also necessary because they lead to loss of BRCA function and altered response to treatment. Studies have shown that patients with both germline and somatic BRCA mutations can have similar positive responses to targeted therapy [7].

BRCA mutation-associated ovarian cancer differs from classic sporadic cases in its molecular and clinical features. Such tumors have higher genomic instability, but at the same time, they are more sensitive to cytotoxic drugs and DNA-damaging therapies. Platinum-based chemotherapy in particular exhibits higher efficacy in patients with BRCA mutations. For example, clinical observations demonstrate that patients with BRCA1 mutations have a stronger initial response to treatment, but there is a risk of relapse. Patients with BRCA2 mutations have a relatively higher overall survival rate. These differences are explained by the specific roles of the BRCA genes in intracellular functions [3].



Graph 1. The effect of BRCA1 and BRCA2 gene mutations on clinical outcomes in ovarian cancer patients [8].

The impact of BRCA1 and BRCA2 gene mutations on treatment response and overall survival in ovarian cancer patients is presented comparatively. As can be seen from Graph 1, the response rate to platinum-based chemotherapy and PARP inhibitors is higher in patients carrying the BRCA1 and particularly BRCA2 mutations than in cases without the mutation. At the same time, patients with BRCA2 mutations have a relatively long overall survival time. These results explain the effectiveness of targeted therapies in relation to the role of BRCA genes in DNA repair mechanisms and form the scientific basis for personalized therapy approaches [8].

3. Clinical Implications and Targeted Therapeutic Approaches

Molecular genetic analysis of BRCA mutations has led to the development of new therapeutic approaches. The most significant of these approaches is the application of PARP inhibitors based on the principle of synthetic lethality. PARP proteins are involved in the repair of single-stranded DNA damage. Blocking the PARP pathway in cells with impaired BRCA function leads to a critical accumulation of DNA damage and tumor cell death. This mechanism is highly effective as a targeted therapy because it does not cause serious damage to healthy cells. Clinical trials reveal that disease-free survival is significantly prolonged in BRCA mutation-carrying ovarian cancer patients treated with PARP inhibitors [9].

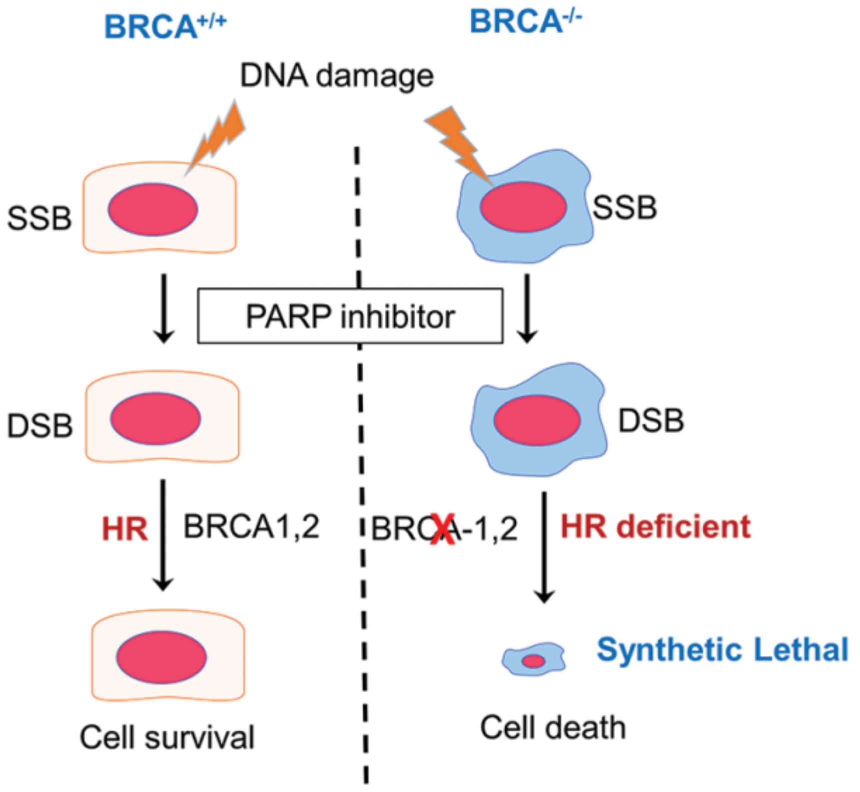


Figure 2. Synthetic lethality mechanism of PARP inhibitors depending on BRCA functional status [10].

The mechanism of action of PARP inhibitors in cells with normal BRCA function ($BRCA^{+}/^{+}$) and cells carrying a BRCA mutation ($BRCA^{-}/^{-}$) is shown comparatively in Figure 2 [10]. In $BRCA^{+}/^{+}$ cells, DNA damage caused by PARP inhibitors is repaired by homologous recombination through BRCA1 and BRCA2, ensuring cell survival. Since $BRCA^{-}/^{-}$ cells lack the homologous recombination mechanism, PARP inhibition causes single-stranded DNA lesions to become double-stranded breaks, and these lesions cannot be repaired. As a consequence, the accumulation of DNA damage at a critical level leads to cell death, a process characterized as the principle of synthetic lethality.

Molecular genetic analysis of the BRCA1 and BRCA2 genes plays a crucial role not only for treatment selection but also in risk assessment and identification of preventive strategies. The application of genetic tests allows for early monitoring of women at risk, planning of preventive surgical interventions, and establishing a personalized medical approach [11].

Thus, the analysis conducted shows that the role of BRCA mutations in ovarian cancer is not only pathogenetic, but also multifaceted in terms of clinical and therapeutic aspects. In-depth study of these genes at the molecular level makes a significant contribution to the development of oncogenetics, the improvement of modern oncological treatment strategies, and the improvement of the quality of life of patients.

4. Conclusion

The analysis demonstrates that the BRCA1 and BRCA2 genes play a central and decisive role in the formation of the molecular-genetic basis of ovarian cancer. These genes act as one of the main mechanisms in maintaining genome stability by ensuring error-free repair of DNA double-strand breaks through homologous recombination. Mutations in the BRCA1 and BRCA2 genes disrupt this protective mechanism, leading to the accumulation of genetic damage in cells, increased chromosomal instability, and ultimately the development of ovarian cancer.

Research results illustrate that BRCA mutations manifest in different forms due to their structural and functional properties, and both their germline and somatic variants are clinically necessary. While germline mutations are hereditary and contribute to the increased incidence of familial ovarian cancer, somatic mutations largely determine the biological behavior of the tumor and its response to treatment. These differences confirm that BRCA mutations have not only pathogenetic but also prognostic value.

Analyses conducted at the molecular-genetic level exhibit that BRCA functional deficiency leads to the formation of new approaches in modern oncological treatment. In particular, PARP inhibitors, based on the principle of synthetic lethality, significantly increase the effectiveness of targeted therapy by inducing selective cell death in BRCA-mutated ovarian cancer cells. Clinical observations reveal that patients with BRCA1 and particularly BRCA2 mutations have a more favorable response to treatment and overall survival rates.

Consequently, in-depth study of the molecular-genetic role and mutation mechanisms of the BRCA1 and BRCA2 genes is of significant scientific and practical importance in terms of early diagnosis of ovarian cancer, identification of risk groups, and implementation of personalized treatment strategies. Research in this area not only contributes to the development of oncogenetics but also allows for the development of more effective and targeted therapeutic approaches in the fight against ovarian cancer.

Author Contributions

The author confirms responsibility for the conception and final approval of the manuscript.

Conflict of Interest

The author declares no competing interests.

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Abbreviations

Breast Cancer 1 Gene (BRCA1), Breast Cancer 2 Gene (BRCA2), Deoxyribonucleic Acid (DNA), Double-Strand Break (DSB), Homologous Recombination (HR), Poly (ADP-ribose) Polymerase (PARP), PARP Inhibitor (PARPi), DNA Repair Protein RAD51 (RAD51), BRCA Wild-Type (Normal BRCA Function) (BRCA$^{+/+}$), BRCA Deficient / BRCA Mutated (BRCA$^{-/-}$), Ovarian Cancer (OC), Hereditary Breast and Ovarian Cancer Syndrome (HBOC), Overall Survival (OS), Progression-Free Survival (PFS), Non-Homologous End Joining (NHEJ).

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