Insights into the role of RUNX1 gene in female-related cancers

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Abstract

The transcription factors of runt-related transcription factor (RUNX) are important regulators of various developmental pathways, with roles in proliferation, differentiation, apoptosis, and cell lineage. One of the core subclasses of the RUNX family that codes for a number of transcription-binding proteins is the RUNX1 gene, which is located on chromosome 21q22.12. There has been extensive research on RUNX1 mutations in hematological cancers, where the most conspicuous position of several chromosomal translocations has drawn interest as a tumor suppressor. In this paper, the malignancies triggered by RUNX1 mutations, which are strongly associated with cancers of the female reproductive system, along with their diagnoses and potential treatments, are reviewed. It has been found that RUNX1 mutation plays a pervasive function in female health, including sex determination, follicular development, steroidogenesis, and the interaction of the estrogen system. In contrast, chromosomal translocations in the gene linked to RUNX1 mutation may lead to severe malignancies in females. Breast, ovarian, uterine, and cervical cancers have shown the highest frequency of genetic abnormalities in the RUNX1 gene. The second most common cause of cancer-related mortality in women is breast cancer, which is also the most common cancer. There is an opposing relationship between uterine cancer and low-grade tumors that often remain confined to the uterus. Due to the regular occurrence of promoter hypermethylation and hypomethylation changes, ovarian cancer has become the most fatal of all gynecological tumors. Finally, despite being the cancer least likely to result from RUNX1 mutation, cervical
cancer can directly impair natural killer cell activity. Both hematopoietic and non-hematopoietic cancer cells can form and become tumors when the RUNX1 gene is mutated, with female malignancies being the primary target. Therefore, more research on RUNX1 gene's pattern of expression, both in vitro and in silico, is needed to lower the incidence of female-related cancers.

Keywords: RUNX1; Chromosomal translocation; Breast cancer; Uterine cancer; Ovarian cancer; Cervical cancer

1. Introduction
Cancer is a disease where cells grow uncontrollably and spread throughout the body, affecting the body’s immune system and eventually all the organs\(^1\). Gynecologic cancer is any cancer that begins in a woman’s reproductive organs. Cervical, ovarian, uterine, vaginal, and vulvar cancers are the five most common kinds of gynecologic cancers\(^2\). According to the data obtained from Cancer Research UK in 2016, breast cancer is the most common female-related cancer in women and has the second highest mortality rate; uterine cancer is the fourth most common cancer in females and has the ninth highest mortality rate in women; ovarian cancer is the fifth most common cancer in women and the sixth most common cause of death in women\(^3\). According to the National Cancer Institute, the estimated number of new breast cancer cases and uterine cancer cases in 2022 is 287,850 and 65,950, respectively, while the estimated deaths of these cases in 2022 are 43,250 and 12,550, respectively\(^4\). The top four cancer-related causes of death in females are expected to see a shift over the next two decades to lung (34,000 deaths), breast (30,000 deaths), pancreatic (22,000 deaths), and uterine (18,000 deaths) by 2040\(^5\). Cancer diagnostics and treatments remain a challenge, because cancer consists of a group of several diseases, and many diverse genetic abnormalities underpin more than 200 different mutations\(^6\). Female-related cancers are caused by several factors, which can be genetic, epigenetic, viral, and environmental\(^7\). Among the susceptible genes, RUNX1 is crucial as it has been found to be associated with most female-related cancers\(^8\). The RUNX family of transcription factors is evolutionarily conserved proteins that play an essential role in fundamental biological processes, including growth and development\(^9\). There are three members (RUNX1, RUNX2, and RUNX3) of the RUNX transcription family in humans, each of which is uniquely expressed in different tissues\(^10\). The RUNX1 gene codes for a human protein, a transcription factor called runt-related transcription factor 1, is also known as acute myeloid leukemia (AML) 1 or core-binding factor subunit alpha-2, which regulates the differentiation of hematopoietic stem cells (HSCs) into mature blood cells\(^11\). The RUNX1 protein binds to specific DNA regions and helps control the function of specific genes. This protein interacts with the core-binding factor subunit beta or CBF\(\beta\) (produced from the CBF-\(\beta\) gene), which, in turn, helps connect it to DNA and inhibits DNA from being degraded (Figure 1). These proteins, collectively, form one version of a CBF\(^12\) homodimer. The RUNX1 protein turns on genes that help control blood cell growth (hematopoiesis)\(^13\). Most research related to females (including breast, ovarian, uterine, and cervical malignancies) indicates a prevalence of RUNX1 gene changes in hormone-associated cancers\(^14\). Mutation in the RUNX1 gene is often found in various hematological malignancies. With the advent of technological revolution, RUNX1 mutation has been proven to play a more pervasive role in cancer than previously believed. Dysregulation of the RUNX1 gene has been reported to be associated with gastric and hepatocellular carcinoma, while single nucleotide polymorphisms (SNPs) in RUNX1 have been linked with human colorectal and prostate cancer\(^15\). In almost 15% of esophageal cancers, RUNX1 mutation tended to be an essential factor for the etiology and development of squamous cell carcinoma in the skin and oral cavity; additionally, strongly focal RUNX1 deletions have been reported\(^22\). RUNX1 gene was first discovered in acute myeloid leukemia gene 1 (AML1) in 1991 as it was linked to the translocation of AML\(^16\). Later in 1993, a murine version of RUNX1 was discovered, leading to the development of RUNX1 knockout mouse models\(^17\). In a screen that was performed to identify mutations affecting segment number and polarity in Drosophila, Nusslein-Volhard and Wieschaus identified the transcription factor RUNX2\(^23\). The mutation that led to defects in pre-segmentation...
patterning and runted embryos was called runt. Later, Gergen et al. cloned the Drosophila segmentation gene runt\textsuperscript{26}. Although the protein encoded by runt was demonstrated to exhibit nuclear translocation, its role as a transcription factor was yet to be established. Eventually, in 1991, the human RUNX1 gene was cloned and observed to be rearranged from t(8;21)(q22;q22) AML patients in leukemic cell DNAs\textsuperscript{27}. However, the role of the human RUNX1 gene had not been identified. The function of the RUNX1 gene was discovered shortly after the discovery of Drosophila runt protein and human RUNX1 protein. As a sequence-specific DNA-binding protein that monitored the disease specificity of the Moloney murine leukemia virus, RUNX1 was purified. Besides, Ito \textit{et al.} purified RUNX2, the RUNX1 homolog. Two subunits, a DNA-binding CBF subunit termed core binding factor $\beta$ (CBF$\beta$), were purified transcription factors; the binding capacity of RUNX1 and RUNX2 was significantly enhanced by the interaction with CBF$\beta$\textsuperscript{28}.

2. \textbf{RUNX1 gene}

2.1. Background of \textit{RUNX1} gene

The human \textit{RUNX1} gene is 260 kilobases (kb) long and is found on chromosome 21 (21\textit{q}22.12)\textsuperscript{29}. The gene can be transcribed from either promoter 1 (distal) or promoter 2 (proximal). As a result of alternative splicing, multiple \textit{RUNX1} isoforms can be generated. The exons encode the full-length RUNX1 protein\textsuperscript{30}. There are two distinct domains among the exons: the runt homology domain (RHD) or runt domain (exons 2, 3, and 4) and the transactivation domain (TAD) (exon 6). RUNX1 requires these domains to facilitate DNA binding and protein-protein interactions, respectively. RUNX1 protein has 453 amino acids. The runt domain (residues 50 – 177), which is homologous to the p53 family, encodes its DNA-binding capabilities as a transcription factor (TF)\textsuperscript{31}.

\textit{RUNX1} is mutated in 4.26% of breast cancer patients, with 1.55% of all breast cancer patients having \textit{RUNX1} mutation\textsuperscript{32}. \textit{RUNX1} is mutated in 0.82% of ovarian cancer patients, with \textit{RUNX1} mutation present in 0.56% of all ovarian cancer patients\textsuperscript{33}. The disruption of gene regulation, which results in the loss or gain of genetic function, is known to play a significant role in carcinogenesis. The addition of a methyl group to cytosine-5 position within the context of a CpG dinucleotide, mediated by DNA methyltransferases, is the most studied epigenetic modification. The natural control of DNA methylation is disrupted in cancer, resulting in dramatic alterations in the distribution pattern of 5-methylcytosine. Heavy methylation in most chromatin is restricted, but unmethylated CpG islands in gene promoters and first exons often become hypermethylated. Aberrant DNA methylation is also implicated in the development of chemotherapeutic resistance. It occurs in ovarian cancer and contributes to carcinogenesis and chemoresistance pathways. In a study, \textit{RUNX1} gene was significantly hypomethylated and overexpressed in post-chemotherapy (CT) primary cultures of ovarian cancer patients\textsuperscript{34}. Using a similar approach (methylated DNA immunoprecipitation coupled to CpG island tiling arrays), the study demonstrated that DNA hypermethylation occurs in less invasive/early stages of ovarian tumorigenesis.

In contrast, advanced disease has been found to be associated with DNA hypomethylation of several oncogenes involved in cancer progression, invasion/metastasis, and likely chemoresistance\textsuperscript{35}. Moreover, according to a study, mutations were observed in \textit{RUNX1} and \textit{CBFB} genes, in which about 8 \textit{RUNX1} mutations were seen within the \textit{RUNX1} coding region in breast cancer cases\textsuperscript{36}. The runt domain, which is crucial for DNA binding and heterodimerization, has all six missense mutations, with four mutations occurring at two mutation hotspots (amino-acid positions 174 and 139/141/142). Notably, all \textit{RUNX1} mutations associated with breast cancer appear to result in loss-of-function mutants\textsuperscript{37}.

2.2. Functions of \textit{RUNX1} gene

Almost all adult mammalian, blood cells develop from HSCs in the bone marrow. HSCs are cells that may engraft adult transplant patients and develop from immature HSC precursors, which are known as pre-HSC. RUNX1 is required for the development of all embryonic blood cell lineages\textsuperscript{27}. The trigeminal and dorsal root ganglia include nociceptors, specialized primary sensory neurons with high stimulus thresholds, and cell bodies. They express various ion channels that convert mechanical, thermal, or chemical inputs into electrical activity\textsuperscript{38}. Several transcription factors regulate the growth of nociceptive sensory neurons. These runt proteins regulate developmental events by interacting with a common cofactor called CBF\textsuperscript{39}. The trigeminal and dorsal root ganglia both express RUNX1 and RUNX3. The \textit{RUNX1} gene is responsible for coordinating the phenotypic of a large number of nociceptors\textsuperscript{39}.

In adult skin, RUNX1 regulates the activation and proliferation of hair follicle stem cells (HFSCs). RUNX1 is found in three types of embryonic skin precursors: short-term hair follicle (HF) progenitors, adult HFSCs, and mesenchymal progenitors\textsuperscript{40}. \textit{RUNX1} gene is required for the development of adult HFSCs and short-term progenitors in the embryonic epithelium, but it is not required either. The \textit{RUNX1} gene is rigidly sought in the embryonic mesenchyme for proper adult HFSC differentiation and long-term skin functioning\textsuperscript{41} (Table 1).
### Table 1. List of some cancer types where RUNX1 gene functions as an oncogene or tumor suppressor gene.

| Function of RUNX1 gene | Cancer type | References |
|------------------------|-------------|------------|
| Oncogenic | Triple-negative breast cancer | [44,48,49] |
| | Ovarian cancer | [34,48,55] |
| | Uterine cancer | [47] |
| | Cervical cancer | [47,55] |
| | Prostate cancer | [47,48] |
| | Colorectal cancer | [47,48] |
| | Skin cancer | [48,55] |
| | Head and neck cancer | [48,56] |
| | Acute myeloid leukemia | [44,57] |
| Tumor suppressor | Breast cancer (excluding triple negative) | [48,58] |
| | Gastrointestinal cancer | [48,59] |
| | Lung adenocarcinomas | [48,60] |
| | Non-small cell lung cancer | [48,49] |
| | Glioblastoma multiforme | [48,61] |
| | Hepatocellular carcinoma | [54,62,63] |
| | Acute lymphoblastic leukemia | [64,65] |

Although the genes associated with cancer development are generally either tumor suppressor genes or oncogenes, the RUNX1 gene can function as both, depending on the context. RUNX genes play a significant role as tumor suppressor genes by inactivating gene mutations, hypermethylation, and deletions in some cancers. While in many other cases, these genes are transcriptionally activated by retroviral insertion, indicating dominant oncogenic potential. The role of RUNX1 gene in tumorigenesis differs with the tumor tissue, type, and stage of tumor development. For instance, the RUNX1 gene plays the role of a tumor promoter in ovarian and skin cancers, but it has been identified as a tumor suppressor in breast (excluding triple negative), lung, and prostate cancers. RUNX1 mutations, which are mostly loss-of-function mutations occurring due to non-sense, frameshift, or missense mutations within the runt DNA-binding domain, take place almost exclusively in the ER-positive, luminal subtype of breast cancer, and pointing to a tumor suppressor role.

On the contrary, enhanced levels of RUNX1 gene expression have been found to be associated with poor outcomes in triple-negative breast cancers (TNBCs), suggesting its role as an oncogenic gene in this breast cancer subtype. Whether the RUNX1 gene acts as an activator or repressor of target gene expression, it depends on the massive number of interacting coactivators, transcription factors, and corepressors. The downregulation of the RUNX1 gene may lead to constitutive gene abnormalities and, thus, result in tumorigenesis, but RUNX1 gene amplification induces gene overexpression or upregulation, which has an immense potential to contribute to the transformation of hematopoietic cells into tumors.

#### 2.2.1. Hematopoiesis

Hematopoiesis occurs during embryonic development and maturity to create and replenish the blood system. Through hematopoiesis research, the mechanisms that lead to blood diseases and malignancies can be better understood by scientists and doctors. HSCs can also be utilized as a model system to study tissue stem cells and their involvement in aging and cancer. HSCs form in the human embryo at 1 month of gestation. However, before HSCs appear, numerous other blood cells develop, some of which are required for embryonic survival and contribute to tissue macrophages in adults. HSCs and hematopoietic progenitors (cells that can develop into various blood cells but do not have long-term multilineage reconstitution capability) arise in three waves, as detailed below. RUNX1 gene is required to differentiate all embryonic blood cell lineages, but it plays a particularly important role in differentiating blood cells from hemogenic endothelium in the second and third waves.

Human embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) have been used to study human hematopoiesis, including the involvement of RUNX1 gene, over the past decade. In a study, human CD34+ CD45+ hematopoietic stem and progenitor cells (HSPCs) were generated from human ESCs and iPSCs about 11–14 days following embryoid body (EB) formation using a feeder-free culture method. Multiple kinds of hematopoietic cells, including myeloid, erythroid, and polyploid megakaryocytic (MK) cells, were formed by CD34+ CD45+ HSPCs. The human iPSCs generated from familial platelet disorder (FPD) patients with heterozygous RUNX1 mutation were similarly found to be deficient in MK production, with the targeted repair of the mutant RUNX1 allele by genome editing restoring MK potential.

Since then, scientists have expanded their research using precise genomic targeting in human wildtype iPSCs to remove excess exon 5 of the RUNX1 gene, shared by all isoforms, produced from the RUNX1a and RUNX1b isoforms, which are mostly loss-of-function mutations occurring due to non-sense, frameshift, or missense mutations within the runt DNA-binding domain, take place almost exclusively in the ER-positive, luminal subtype of breast cancer, and pointing to a tumor suppressor role.
KO of RUNX1 at exon 5 (ablating all three isoforms) did not affect the development of CD34+/CD31+/CD144+ endothelial-like cells. However, no CD45+ hematopoietic cells developed from the endothelial-to-hematopoietic transition (EHT) culture that was treated with hematopoietic cytokines, indicating that the EHT was fully inhibited[27].

2.2.2. Nociceptive sensory neurons regulation

The transduction of noxious stimuli triggers the interpretation of pain in mammals through specialized ion channels and receptors expressed by nociceptive sensory neurons[79]. However, the molecular mechanisms responsible for specifying different sensory modalities remain poorly understood. RUNX1, a runt domain transcription factor, is expressed in most nociceptors during embryogenesis. RUNX1 controls the expression of several ion channels and receptors in these neurons, namely, thermal receptors of the transient receptor potential (TRP) class, Na+-gated, ATP-gated, and H+-gated channels, μ-opioid receptor (MOR), and protein-coupled receptors of Mas-related G-protein-coupled receptor (Mrgpr) class G[71].

RUNX1 also regulates the lamina-specific innervation pattern of the spinal cord’s nociceptive afferents. In addition, mice that lack RUNX1 show certain defects in thermal and neuropathic pain[72], thus suggesting that the phenotype is coordinated by RUNX1. This finding has implications for pain treatment of a broad cohort of nociceptors. The mammalian genome encodes three runt domain transcription variables: RUNX1, RUNX2, and RUNX3. These runt proteins interact with CBFβ cofactor to regulate several developmental processes[73]. The trigeminal and dorsal root ganglia both express RUNX1 and RUNX3. It appears that RUNX1 expression is limited to nociceptors; the persistent RUNX1 gene expression labels nociceptors undergoing the developmental transition from TrkA to Ret. The transition from TrkA to Ret is disrupted in mice that selectively lack RUNX1 gene function in the peripheral nervous system[74]. Besides, we find that activating or suppressing the expression of a significant number of nociceptive ion channels and sensory receptors requires RUNX1 molecules.

Moreover, the RUNX1 gene is necessary for the dorsal spinal cord to target afferent projections to the specific lamina[75]. Ultimately, behavioral research has demonstrated certain deficits in thermal and neuropathic pain in RUNX1-deficient mice. These results indicate that the phenotype of a broad collection of nociceptors is coordinated by RUNX1 molecules[40].

2.2.3. Hair follicle development

RUNX1 genes also regulate HFSC activation and proliferation in adult skin[74]. RUNX1 gene expression is most common in the mesenchymal and epithelial compartments in hair follicles, where the three RUNX proteins are expressed[27]. The epithelial expression involves hair keratin, which forms layers of the hair shaft and the bulge. The RUNX1 gene is notably coexpressed with keratin 15, which is a marker of hair follicle stem cells. RUNX1 gene is expressed in a distinct dermal sub-epithelial layer in the hair mesenchyme during the initial stages of hair morphogenesis. At the same time, it is located in the dermal papilla at later stages in a hair cycle-dependent pattern. In experiments on knockout mice, the RUNX1 gene was found to be expressed in several hair follicle chambers, along with the bulge and germ, but not in other skin epithelial structures, such as the sebaceous gland and the epidermis. The structure of the hair shaft, the activation of HFSC, and the onset of anagen are all affected by constitutive epithelial deletion of RUNX1 gene through development. Besides, the role of RUNX1 gene in skin cancers is yet to be explored[74]. It is necessary to clarify this stance because skin cancer is the most common human malignancy and HFSC is a well-recognized source of skin appendage tumors, such as basal cell carcinoma (Table 2).

3. RUNX1 gene and female health

3.1. Sex determination

Sex determination is the process through which sexually reproducing organisms differentiate as male or female[79]. Although the process varies extensively between different organisms, numerous species have shown a physiological link between the RUNX1 gene and the development of female reproductive tissues. Conceivably, this link was studied for the first time in Drosophila melanogaster. It can be seen that the runt gene is required to express Sex-lateral gene in the blastoderm embryo, which is responsible for maintaining the on/female mode or off/male mode[60,81]. In mammals, the RUNX1 gene was found to be strongly expressed in the ovarian stroma, suggesting that it is indeed related to female sex development[82]. RUNX1 protein was also detected in oocytes and granulosa cells of preantral follicles and theca cells of antral follicles. This was further bolstered by the fact that RUNX1 is a Wnt-4 signaling target gene[83]. The absence of Wnt-4 results in partial reverts of a female embryo into a male embryo. In addition, Wnt-4 also suppresses testosterone-related genes, promotes the maturation of the Mullerian duct, and triggers the production of female germ cells. The knockout of Wnt-4 causes a reduction in RUNX1 gene expression, suggesting that the RUNX1 gene might play a crucial role in ovary organogenesis[84]. A significant expression of the RUNX1 gene in the ovaries of various species (human, goat, mice, and trout) during early gonad differentiation indicates an evolutionarily conserved role of the gene in ovary differentiation.
3.2. Follicular development and steroidogenesis

RUNX1 also plays pivotal roles in follicular development and steroidogenesis. According to research, it plays a role in the production and survival of peri-ovulatory follicles in rat ovaries[85,86]. Studies have shown that RUNX1 protein is expressed particularly in granulosa cells of pre-ovulatory follicles in rat ovaries following human chorionic gonadotropin (hCG) injection, which stimulates ovulation through luteinizing hormone (LH) surge (Figure 2)[87]. A similar result was observed in bovine follicles, where RUNX1 gene was significantly upregulated by an LH surge in theca[88]. This aggregated evidence suggests that RUNX1 gene might be hormonally regulated. It has also been observed that the reduction of RUNX1 mRNA expression leads to a decrease in progesterone production. Moreover, the knockdown of RUNX1 gene significantly decreases estradiol levels and several other steroidogenic enzymes in granulosa cells, such as cytochrome P450 family 11 subfamily A member 1 (CYP11A1), which is responsible for progesterone synthesis (Figure 2). However, the exact stage of follicular development in which hCG injection causes an increase in RUNX1 expression has yet to be elucidated. Several studies have shown that it solely involves the LH-activated adenylate cyclase-mediated signaling pathway, while others have suggested that it involves protein kinase C (PKC) and P13K pathways[89]. Therefore, further studies are required to achieve definitive results.

3.3. Estrogen pathway interplay

Naturally, RUNX1 and its relation to the estrogen-estrogen receptor (ER) pathway significantly contribute to female sex development, given that estrogen is the primary female sex hormone. It is essential for the function and development of female reproductive tissues, mammary cell division, etc. Most estrogen activity is mediated by ER, which can be further classified into ER alpha (ERα) and ER beta (ERβ); ERα and ERβ are isoforms of each other, formed from separate genes[90]. Initially, estrogen response was thought to be the classical estrogen pathway, which solely depends on ligand activation, but, further, research has led to more pathway mechanisms, including ligand-independent ER activation, non-genomic activation, and ER element (ERE)-independent activation[91]. The mechanism of the putative role of RUNX1 gene in the ER pathway has not been elucidated; however, some links have been deduced between the two (Figure 3).

3.4. Uterine development

In mice, the RUNX1 gene is significantly expressed in the uterus’s luminal and glandular epithelia and immune cells. Interestingly, studies in different mouse strains showed significant upregulation of RUNX1 gene when exposed to estradiol. Based on a study that demonstrated estradiol-induced cellular responses in mouse models with greater RUNX1 gene expression, it has been suggested that RUNX1 enhances estradiol, and thus uterine development[92]. Estradiol is the primary estrogen steroid female sex hormone that regulates the estrous and female menstrual cycles. This suggests that ERα might regulate gene expression by binding to RUNX1 (where RUNX1 acts as a tethering factor)[93]. RUNX1 mediates ERα localization in the chromatin and has been identified as a mediator of ERE-independent estrogen signaling[84].
estradiol to the tethered pathway often prevents increased uterine function\(^95\).

In contrast, the tethered/non-ERE pathway is a typical uterine transcriptional response to estradiol\(^95\). It can be deduced from this that \(\text{RUNX1}\) gene plays a role in uterine development, even when a tethered/non-ERE pathway is used. Collectively, this concludes that \(\text{RUNX1}\) has a putative role in epistatic interactions that lead to genetic variations in the responsiveness of the uterus to estradiol. However, further research is needed to fill the knowledge gaps of how this has a role in inheritance.

### 3.5. Mammary gland functioning

Mammary cells arise from the ectodermal bud and undergo postnatal ductal development to form alveolar structures up to lactogenesis after pregnancy\(^98\). Estradiol is a crucial regulator of this development. It acts on \(\text{ER}\)α found in the stroma and epithelium of mammary cells. \(\text{ER}\)α has been reported to play a role in the differentiation and proliferation of mammary cells\(^90\). Hence, \(\text{ER}\)α is essential for the development of the adult mammary gland. Studies have shown that \(\text{ER}\)α knockout leads to underdeveloped mammary glands in mice\(^98\). Genome-wide maps specific to \(\text{ER}\)-binding sites have shown that \(\text{ER}\)α tethering requires the \(\text{RUNX1}\) transcription factor.

Moreover, \(\text{RUNX1}\) genes are usually present in the mammary gland. Their expression levels vary during different stages of pregnancy, lactation, and the female reproductive cycle. This reflects their specific roles in mediating mammary gland function. The \(\text{RUNX1}\) protein is mainly found in the basal and luminal cell layers of epithelial cells\(^99\). On the contrary, there is lower expression of normal \(\text{RUNX1}\) gene in breast cancer cells, indicating that \(\text{RUNX1}\) is essential for healthy cell proliferation, and sustaining the pivotal role of \(\text{RUNX1}\) in the mammary gland.

### 4. Impact of \(\text{RUNX1}\) mutation

Chromosomal translocations are a specific type of mutation, in which abnormal exchanges occur between homologous chromosomes. According to numerous studies related to different forms of cancers, the \(\text{RUNX1}\) locus is a common site for multiple chromosomal translocations. Monoallelic point mutations such as the one that results in the loss of \(\text{RUNX1-}\text{MTG16}\) contribute to breast cancer.

\(\text{RUNX1-}\text{MTG16}\) protein is the result of a fusion between the \(\text{RUNX1}\) at its N terminus (truncated at the runt domain) to the C terminus of \(\text{MTG16}\) protein that plays a part in tumor suppression due to t(16;21) (q24;q22) translocation. This results in the loss of \(\text{MTG16}\) tumor suppressor function through heterozygosity in breast neoplasms at 16q24- resulting in breast cancer\(^100\). Moreover, the \(\text{RUNX1}\) gene is downregulated in cancer cells at the metastasis stage and thought to be a tumor suppressor\(^101\).

Other aberrations in this gene lead to different cancers with varying percentages of alteration frequencies (genes altered per case), some of which include acute myeloid leukemia (13.5%), esophageal cancer (8.24%), breast cancer (6%), and colorectal cancer (3.03%)\(^102\). Absolute counts of these mutations showed that hormone-related female cancers are prevalent with relatively high aberrations compared to male-related cancers (Table 3).

### 5. Role of \(\text{RUNX1}\) gene mutation(s) in female-related cancers

#### 5.1. Breast cancer: Overview and development

Whole-genome/exome sequence studies have reported that point and deletion mutations in \(\text{RUNX1}\) gene could result in ER-positive, luminal, and basal subtype of breast cancer\(^104\). Besides, it has been found that \(\text{RUNX1}\) knockdown may cause hyperproliferation and abnormal morphogenesis of the human mammary epithelial cell line (MCF10A)\(^112\). Moreover, a Moroccan study found that \(\text{RUNX1}\) SNPs were firmly correlated with breast cancer risk\(^113\).

On the other hand, several experiments have indicated that the \(\text{RUNX1}\) gene plays a pro-oncogenic role in breast cancer, which is interestingly related to the ER-negative and triple-negative (TN) subtypes. Different transcriptome studies have reported that \(\text{RUNX1}\) mRNA is significantly upregulated in the TN subtype group\(^114\). At the same time, the \(\text{RUNX1}\) gene has been found to be correlated with
super-enhancer elements that are connected to oncogenes and genes associated with cancer pathogenesis, precisely in an ER-negative breast cancer cell line\textsuperscript{116}. In another study, RUNX1 gene was found to be highly expressed with disease progression in patient samples and a mouse model of breast cancer\textsuperscript{35}. \textsuperscript{117}

RUNX1 has recently been recognized as a novel mutated gene in human luminal breast cancer. It is expressed in all murine mammary epithelial cells (MECs) subpopulations, except for secretory alveolar luminal cells. Moreover, a decrease in luminal cells is observed due to the conditional knockdown of RUNX1 in MECs by MMTV-Cre. The reason behind this is the significant reduction of the ER-positive, mature luminal subpopulation. A master regulatory transcription factor for alveolar cells, Elf5, is repressed by RUNX1. The \textit{RUNX1} gene also regulates mature luminal TF/co-factor genes (\textit{e.g.}, \textit{FOXA1} and \textit{CITED1}) that are involved in the ER program (\textit{Figure 4}). Besides, it is possible that the \textit{RUNX1} gene also contributes to the loss of the cell-of-origin of luminal breast cancer, as its disruption reduces the ER-positive luminal MECs from where cancer originates\textsuperscript{117}. Since a decrease in \textit{RUNX1} expression leads to an increase in breast cancer aggression, higher levels of \textit{RUNX1} expression are associated with good prognosis\textsuperscript{103}. However, an excessive expression of \textit{RUNX1} might be oncogenic as well. It has been found that in luminal breast cancer, four missense mutations take place in the \textit{RUNX1} gene, of which three are located in the runt domain, gathered within the putative ATP-binding site, which contains eight amino acid residues\textsuperscript{44}. Various studies have revealed \textit{RUNX1} suppression of breast cancer epithelial-to-mesenchymal transition and \textit{RUNX1} repression of cancer stem cells and tumor formation\textsuperscript{8}. Apart from that, in many other studies, \textit{RUNX1} seemed to show monoallelic point mutations in different luminal and basal levels of human breast cancer\textsuperscript{118}.\textsuperscript{8}

\textbf{5.2. Uterine cancer: Overview and development}

According to the well-accepted dualistic model of endometrial tumorigenesis, uterine or endometrial cancer is generally classified into two major types based on histological and clinical characteristics, that is, endometrioid endometrial carcinoma (EEC) and non-endometrioid endometrial carcinoma\textsuperscript{106}. Intriguingly, \textit{RUNX1} appeared as one of the most highly upregulated genes from a list of 53 differentially expressed cDNA targets, while comparing gene expression profiles of normal versus EEC tissues\textsuperscript{109}. Various studies have revealed \textit{RUNX1} suppression of breast cancer epithelial-to-mesenchymal transition and \textit{RUNX1} repression of cancer stem cells and tumor formation\textsuperscript{8}. Apart from that, in many other studies, \textit{RUNX1} seemed to show monoallelic point mutations in different luminal and basal levels of human breast cancer\textsuperscript{118}.\textsuperscript{8}

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\begin{tabular}{|l|l|l|l|}
\hline
Cancer type & \textbf{RUNX1 mutation} & Tumor stage/type & References \\
\hline
Breast cancer & Silent & Luminal B (ER-positive) & \textsuperscript{35,103} \\
& Missense & Luminal B & \textsuperscript{49} \\
& Homozygous deletion & Luminal A and B & \textsuperscript{104} \\
& Monoallelic point & Luminal A and B & \textsuperscript{8} \\
& Frameshift & Luminal A and B & \textsuperscript{44} \\
& Non-sense & Luminal A and B & \textsuperscript{49} \\
& Deletion & Luminal and basal & \textsuperscript{44} \\
& Chromosomal translocation & - & \textsuperscript{99} \\
& Mutation (driver) & Luminal and basal & \textsuperscript{44} \\
\hline
Uterine cancer & Substitution & Endometrioid carcinoma & \textsuperscript{105} \\
& mRNA upregulation & Endometrioid carcinoma & \textsuperscript{106} \\
& mRNA upregulation & Myometric & \textsuperscript{106} \\
& Chromosomal translocation & Endometrioid carcinoma & \textsuperscript{106} \\
& Heterozygous point & Endometrioid carcinoma & \textsuperscript{107} \\
\hline
Ovarian cancer & mRNA upregulation & Epithelial ovarian cancer & \textsuperscript{8} \\
& Point & Epithelial ovarian cancer & \textsuperscript{108} \\
& mRNA downregulation & Epithelial ovarian cancer & \textsuperscript{109} \\
& Deletion & Epithelial ovarian cancer & \textsuperscript{110} \\
& mRNA upregulation & Epithelial ovarian cancer & \textsuperscript{110} \\
\hline
Cervical cancer & NK cell cytotoxicity & Squamous cell carcinoma, adenocarcinoma & \textsuperscript{111} \\
\hline
\end{tabular}
\caption{Summary of \textit{RUNX1} gene mutations that lead to the development of different female-related cancers.}
\end{table}
factor, whose expression also seemed to be upregulated during the primary steps of EEC progression. Moreover, high levels of matrix metalloproteinase (MMP)-2 and -9 expression have also been found to colocalize with ERM/ETV5 and RUNX1 at the invasive front of endometrial cells, encouraging an interplay between these proteins during myometrial infiltration\cite{120,121}. Besides, the RUNX1 gene is also strongly associated with the expression of the double-strand-break repair protein rad21 homolog (RAD21), a crucial component of the cohesin complex that is involved in chromosome segregation and often dysregulated in solid tumors of the breast and ovary\cite{122,123}. Surprisingly, experiments in zebrafish have revealed that RAD21 is a regulator of RUNX1 gene (Figure 5).

In a study, RUNX1 levels were significantly increased in circulating tumor cells (CTCs) that were isolated from high-risk EEC patients presenting with more than 50% of myometrial infiltration. Besides, ectopic RUNX1 gene expression increased the rate of metastasis in an orthotopic endometrial mouse model, implicating the gene as a putative inducer of metastasis\cite{105}. Therefore, RUNX1 is a pro-oncogenic player in uterine cancer. The mutations observed in RUNX1 gene are mostly due to myometrial infiltration, substitution, mRNA upregulation, or in very few cases, heterozygous point mutations\cite{107}. EEC, or type I endometrioid endometrial carcinoma, is one of the two types of uterine cancer, in which the gene expression profile of RUNX1 has the highest value.

5.3. Ovarian cancer: Overview and development

Of all the female gynecological malignancies, ovarian cancer is the deadliest one. Its treatment is also complicated. According to the World Health Organization (WHO), each year, an estimated total of 140,200 patients are diagnosed with ovarian cancer, representing the 7th most common form of cancer and the 8th leading cause of cancer-

![Figure 4. Formation of breast cancer by different mutated pathways of RUNX1.](image)

![Figure 5. Formation of uterine cancer by different mutated pathways of RUNX1.](image)
related deaths in women worldwide\cite{124,125}. Moreover, around 300,000 new cases of ovarian cancer occur every year according to the World Cancer Research Fund\cite{126}. Most tumors in this particular malignancy are usually diagnosed at a very late stage when patients present with upper abdominal and distant metastases. In such cases, life-saving surgery cannot be performed\cite{127}. The disease may be caused by various genes being overexpressed, under-expressed, or even subjected to epigenetic changes besides somatic mutations\cite{128}. In a study, hypomethylation was observed in 46 putative oncogenes in the primary cell culture, where a high occurrence of RUNX1 mutation was detected in ovarian cancer progression\cite{3}. Immunohistochemical analysis showed that RUNX1 gene expression was significantly higher in high malignant potential and low malignant potential tumors, as well as in omental metastasis, compared to normal ovary\cite{34}. Another report demonstrated that short hairpin (sh)RNA-mediated RUNX1 knockdown significantly impacted the proliferative and migratory ability of ovarian cancer-causing SKOV3 cells (Figure 6). Similarly, RUNX1 mRNA upregulation and RUNX1 protein overexpression are known to decrease miR-302b and increase the risk of ovarian cancer\cite{110}. A reduced miR-302b can regulate RUNX1 pro-oncogenic activity, leading to signal transducer and activator of transcription 3 (STAT3) signaling pathway\cite{129}. Likewise, in the case of ovarian cancer, it can have the same effect by activating invasive phenotypes by MMP-2 and MMP-9 signaling pathways\cite{130}. Therefore, all the dysfunctional evidence hints at the correlation between the oncogenic functionality of RUNX1 gene and a potential prognostic biomarker for developing ovarian cancer in the female population. A carcinoma cell biopsy followed by immunohistochemical analysis revealed significant upregulation of the RUNX1 gene compared to the control, suggesting the use of RUNX1 gene as a biomarker for ovarian cancer diagnosis\cite{3}.

5.4. Cervical cancer: Overview and development

Cervical cancer rates vary across the world, with Eastern Africa having the highest rate and Western Asia having the lowest. According to the WHO, it is the fourth most common type of cancer in women and a major cause of cancer-related deaths among low- and middle-income countries. In 2020, an estimated 604,237 women were diagnosed with cervical cancer globally, representing 6.5% of all female cancers\cite{131}; new cases of cervical cancer have been estimated to be around 14,100 in 2022, with 4280 deaths\cite{132}. One of the significant kinds of adenocarcinoma, developed from the influence of RUNX1, is the cervical that occurs in the ectocervix. In the lower Mullerian duct (MD), epithelial cells are obligated to become stratified squamous epithelium of the ectocervix and vagina, as the expression of ΔNp63 transcription factor is induced by vaginal mesenchyme\cite{111}. In the MD epithelium (MDE), SMAD4 gene is essential for the activation of ΔNp63. This transcription factor binds on the 5′ sequence adjacent to the transcription start site (TSS) of ΔNp63 in the future vaginal epithelium (VgE)\cite{133}. This SMAD-dependent activation of the ΔNp63 locus requires the expression of RUNX, which activin A (ActA) activates through a SMAD-independent mechanism\cite{134}. The ActA-RUNX1 pathway is independently required for the vaginal cell fate commitment of MDE. Inactivation of it in MDE results in uterine epithelial differentiation of MDE within the vagina, a congenital epithelial lesion called vaginal adenosis\cite{133}. Vaginal adenocarcinomas (VACs) or cervical cancers are believed to arise from vaginal adenosis due to adenosis lesions at the primary site of VACs\cite{135}. According to cBioPortal for Cancer Genomics, the RUNX1 gene shows 2.3% genetic perturbations in cervical cancers. In their report, the genetic alterations of RUNX1, including amplification of 1%, deep deletion of 2%, and missense

Figure 6. Formation of ovarian cancer by different mutated pathways of RUNX1.
mutation (putative passenger) of 2.3%, have been documented in cervical cancer\cite{136,137}. Several studies have concluded that micro (mi)RNAs could function as a major oncogene or tumor suppressor of various cancers by reprogramming NK cell-mediated cytotoxicity to tumor cells by different mechanisms\cite{138,139}. miR-20a is a widely known oncomiR that is associated with the development of cervical cancer\cite{140}. In a study, the RUNX1 gene was identified as a direct target of miR-20a, inhibiting the killing effect of NK cells to cervical cancer cells by negatively regulating RUNX1 gene expression (Figure 7)\cite{141}. There is emerging evidence showing that RUNX1 gene is highly expressed in NK T-cells and CD4 T-cells and is associated with NK differentiation. Cells participate in the progression of cervical cancer through the modulation of NK\cite{142}. Treatment for cervical cancer, which includes surgery, radiation, and chemotherapy, depends on the stage of cancer, patients’ health issues, and their personal preferences. Surgeries might include only removing the carcinoma if the cancer is at the first stage. Immunotherapy and drug-based treatments are also potential therapies, where cell-mediated drugs and various inhibitors against RUNX1 gene are used to treat cervical cancer\cite{143}.

### 6. Conclusion

Both hematopoietic and non-hematopoietic cancer cells develop and undergo tumorigenesis as a result of RUNX1 mutation or overexpression. However, the role of RUNX1 gene in the activation or inhibition of different tumor cell growth is still unknown, which leaves room for additional research. Chromosomal abnormalities result in gene mutations, which have a statistically significant association with non-hematopoietic cancer in women in particular. In addition, the interaction of RUNX1 gene with the estrogen-ER pathway shows that it has a tight connection with female reproductive development. Female health and reproduction are particularly vulnerable to disorders brought on by the RUNX1 gene. Since the dawn of humanity, technology has been constantly improving and changing, and medical discoveries have not lagged behind. Even now, the number of diagnostic facilities, equipped with cutting-edge technology that speeds up the process and produces precise findings, is growing. Therefore, identifying mutations in malignancies, particularly those linked to RUNX1 disorders, have become much more effective. Every day, there are improvements in therapies, and genomic sequences are employed as guidelines for drug development. As a result, RUNX1 mutations are now easy to identify and treat.

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