International Journal of Pharmaceutical research and Applications
Volume 10, Issue 4, Jul.-Aug. 2025, pp:529-536 www.ijprajournal.com ISSN: 2456-4494

A Review on Cancer Stem Cell Biomarkers and Related Signalling Pathways.

Akshaya.S.S *[1], Dr. Kiran K.J[2], Dr. Prasobh G.R[3]

1. *Student , seventh semester B Pharm , Sree krishna college of pharmacy and research centre , Parassala , Thiruvananthapuram , Kerala, India -695502
2. Vice Principal , Sree Krishna College of pharmacy and Research centre, Parassala , Thiruvananthapuram , Kerala, India-695502
3. Pincipal, Sree Krishna College of pharmacy and Research centre , Parassala , Thiruvananthapuram , Kerala, India- 695502

Date of Submission: 20-07-2025 Date of acceptance: 02-08-2025

ABSTRACT:
Tumor-initiating cells (TICs), another name for cancer stem cells (CSCs), are cancer cells with the capacity to proliferate, differentiate, and self-renew. Although it is generally accepted that CSCs are essential for the development, spread, and recurrence of malignancies, it is still unknown where CSCs come from. Cell fusion and horizontal gene transfer, which can happen during development and tissue healing processes, are thought to be significant origins of CSCs, according to a number of theories that have been proposed thus far. Furthermore, the cell microenvironment plays a crucial role in the self-renewal and differentiation of CSCs, and crucial gene alterations in stem cells, progenitor cells, or even differentiated cells may also aid in the development of CSCs.

KEYWORDS: Cancer, Cancer stm cell , biomarkers , Signalling pathway.

I. INTRODUCTION :

Cancer are a group of disease characterised by uncontrolled growth and spread of abnormal cells. If the spred of cancer cell this stage is called metastasis is not controlled it can result in death . Caner is caused by many external factors (tobacco , radiation , chemicals)as well as some intenal factors (inherited mutation , hormones , immune condition)[1]

The name cancer derived from an observation by "Hippocrates "more than 2,300 years ago. The term " Korkinoma " in Greek came then cancer in Latin .[2] Cancer is the largest group of disease with one in common . They happen when normal cell become cancerous cell .your gene send instruction to the cell – like when to start and stop growing . Example normal cell follow the instruction but the cancer cell ignore the instruction . The most common type of cancer in males are Lung cancer , prostate cancer , colorectal cancer and stomach cancer . In females, the most common type of cancer are breast cancer, colorectal cancer , lung cancer and cervical cancer .[3] In children acute lymphoblastic leukemia and brain tumor [4].

It is anticipated that there will be 1392,179 cancer patients in India by 2020 and 1569,793 by 2025. In Delhi the northern region of India , the incidence rates of tobacco – related malignancies were high (62.1% for men and 18.5% for women).

TYPES OF CANCER :

- **On the basis of origin :**
  By primary site of origin , cancers maybe of specific types like
  - Bladder cancer
  - Thyroid cancer
  - Breast cancer
  - Prostate cancer
  - Pancreatic cancer
  - Liver cancer
  - Renal cancer
  - Lung cancer
  - Skin cancer
  - Brain cancer .[5]
- **On the basis of tissue :**
  Based on tissue type caner can be categorized into six categories
  - Carcinoma
  - Sarcoma
  - Myeloma
  - Leukemia
  - Lymphoma
  - Mixed types

- **Carcinoma :**
  It is the cancer which is found in the tissue known as " Epithelial tissue "that covers

International Journal of Pharmaceutical research and Applications
Volume 10, Issue 4, Jul.-Aug. 2025, pp:529-536 www.ijprajournal.com ISSN: 2456-4494

surface of organs , glands or body structure and there are four main types of carcinoma they are melanoma , basal cell carcinoma , squamous cell skin cancer and merkel cell carcinoma

- **Sarcoma :**
  It is a malignant tumor growing from connective tissue such as cartilage , fat , muscles , tendons and bones . Most common sarcoma is of bone. Eg : Osteosarcoma (occurs in bone), Chondrosarcoma (occurs in cartilage) , Rhabdomyosarcoma (occurs in skeletal muscle), Liposarcoma (occurs in fatty tissue).
- **Lymphoma :**
  The cancer originated in the nodes or glands in the lymphatic system there are three types of lymphoma they are Hodgkins lymphoma , non – Hodgkin 's lymphoma and cutaneous lymphoma .
- **Leukemia :**
  Also called as "Blood cancer "or cancer of bone marrow , that keeps bone marrow from producing normal red and white blood cells and platelet .
- **Myeloma :**
  It grows in the plasma cells of bone marrow , in some cases the myeloma cells collect in one bone and forms a single tumors that is called a plasmacytoma . In some other causes the myeloma cells collect in many bones , forming many bone tumors , that is called multiple myeloma . [6]

CAUSES :

- **Chemical cacinogens :**
  Examples include cigarette smoke, asbestos, alcohol, air pollution, and certain chemicals found in contaminated food and drinking water. These are substances that, when encountered, can potentially lead to cancer.
- **Biological carcinogens :**
  This category involves viruses, bacteria, and parasites that are linked to an increased risk of cancer development.[7]

DIAGNOSIS :

- **Biospy :**
  A biopsy is a medical procedure in which a tissue sample is taken from the area of suspicion and viewed under a microscope.To help confirm the diagnosis, pathologists examine the tissue sample to look for cancer cells.
- **Histopathological study** :
  Tissue samples are examined under a microscope as part of histopathological investigations. In order to identify aberrant cellular alterations suggestive of malignancy, pathologists examine these samples. This method is essential for comprehending the properties of malignant tissues.
- **Radiography techniques :**
  Radiography techniques, including X-rays, are frequently used to take images of afflicted areas in the body. These images aid in the identification of abnormalities, such as tumors or irregular masses that may be suggestive of radiography cancer.
- **Magnetic resonance imaging :**
  Another imaging method that offers high-resolution pictures for evaluating malignancy, particularly in soft tissues, is magnetic resonance imaging (MRI). It provides outstanding contrast and is very useful for spotting anomalies in different body areas.[8]

STAGES :

- **Stage I:**
  There is no indication that the cancer has spread to neighboring lymph nodes or other tissues; instead, it is contained in a small, localised location.
- **Stage II:**
  Although there has been some growth, the cancer has not spread to other parts of the body and is still confined.
- **Stage III:**
  The cancer has spread, potentially affecting neighboring lymph nodes or other parts of the body; this is known as metastatic cancer.
- **Stage IV:**
  Often referred to as metastatic cancer, this advanced stage shows that the cancer has spread to another organ or remote part of the body.[9]

TREATMENT :

- **Surgery :**
  Removing as many cancer cells as possible is the aim of surgery. Patients must also be satisfied with the surgical outcome in terms of quality of life issues like dysfunction.
- **Chemotherapy :**
  Chemotherapy uses of drugs to kill cancer cell . The ideal chemotherapeutic agent would preferentially target cancer cell , by virtue of their genetic makeup , increased blood flow or high oxygen consumption , while sparing normal cell .[10]

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CANCER STEM CELL :

Cancer stem cell represents specific type of rare cells found in broad majority of tumors , possessing self renewal and differentiation capacities . They contribute to the heterogeneous lineages of cancer cells that form the tumor and share some of the common characteristics with stem cells. [11]

In 1997 , Dominique Bonnet and John E. Dick were the first to identify CSCs from mononuclear cell of the blood of human acute myeloid leukemia . They explained that these cells share similar characteristics with the normal stem cell (NSC).[12]

Three distinctive properties of cancer stem cells are

- Renewal
- The ability to develop into multiple lineages .
- The potential to multiply quickly [13]

ORIGIN :

Hypothesis :

According to the "mutation in stem cell niche populations during development" theory, these developing stem populations undergo mutations, which are then passed on to numerous offspring. The likelihood of a malignant mutation is increased by the quantity of these daughter cells, which are considerably more likely to develop into tumors.[14]

Adult stem cell :

Another theory links the development of tumors to adult stem cells (ASC). This is most frequently linked to tissues (such the skin or gut) that have a high rate of cell turnover. Because of their long lifespan and frequent cell divisions (in contrast to most ASCs), ASCs are candidates in these tissues. Mutation accumulation is the main cause of cancer initiation, and this combination produces the perfect environment for mutations to accumulate. Even if certain malignancies have been connected to particular causes, evidence suggests that the correlation is a real event.[15]

De-differentiation :

De-differentiation of mutated cells may create stem cell-like characteristics, suggesting that any cell might become a cancer stem cell. To put it another way, a fully differentiated cell returns to a stem-like state through mutations or extracellular Most recently, this idea has been illustrated in models of prostate cancer, where cells receiving androgen deprivation therapy seem to temporarily change their transcriptome to resemble neural crest stem cells, which have the invasive and multipotent characteristics of this type of stem-like cell.[16]

CSC BIO-MARKERS :

- CD133 (prominin 1) is a five-transmembrane domain glycoprotein expressed on $CD34^+$ stem and progenitor cells, in endothelial precursors and fetal neural stem cells. It has been detected using its glycosylated epitope known as AC133.
- EpCAM (epithelial cell adhesion molecule, ESA, TROP1) is hemophilic Ca^{2+}-independent cell adhesion molecule expressed on the basolateral surface of most epithelial cells.
- CD90 (THY1) is a glycosylphosphatidylinositol glycoprotei n anchored in the plasma membrane and involved in signal transduction. It may also mediate adhesion between thymocytes and thymic stroma.
- CD44 (PGP1) is an adhesion molecule that has pleiotropic roles in cell signaling, migration and homing. It has multiple isoforms, including CD44H, which exhibits high affinity for hyaluronate and CD44V which has metastatic properties.
- CD24 (HSA) is a glycosylated glycosyl phosphatidylinositol-anchored adhesion molecule, which has co-stimulatory role in B and T cells.
- CD200 (OX-2) is a type 1 membrane glycoprotein, which delivers an inhibitory signal to immune cells including T cells, natural killer cells and macrophages.
- ALDH is a ubiquitous aldehyde dehydrogenase family of enzymes, which catalyzes the oxidation of aromatic aldehydes to carboxyl acids. For instance, it has a role in conversion of retinol to retinoic acid, which is essential for survival.[17]

SIGNALLING PATHWAY INVOLVED IN CSC :

Numerous tightly controlled molecular signaling pathways in normal stem cells support their diverse characteristics, including self-renewal, survival, proliferation, and differentiation. Furthermore, a variety of endogenous and foreign genes, microRNAs, regulatory elements, and extrinsic and intrinsic molecular signals control these intricate pathways. These pathways, which control and enhance the activity of CSCs, are intricate networks of signaling mediators rather than being linear. To date, nine signaling pathways have been

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Volume 10, Issue 4, Jul.-Aug. 2025, pp:529-536 www.ijprajournal.com ISSN: 2456-4494

identified as being involved in both cancer and embryonic development. Merely seven of these nine pathways—including the JAK/STAT, NOTCH, NF-κB, TGF-β, and Wnt pathways—are shared by both cancer and stem cells.

- **Hedgehog signalling pathway :**

Extracellular Hh ligands, the transmembrane protein receptor (PTCH), a transmembrane protein (SMO), an intermediate transduction molecule, and the downstream molecule GLI make up this intricate signaling network. SMO protein has a positive regulatory function in the system, whereas PTCH has a negative regulatory function [18]

The functions of the various GLI subtypes vary, with Gli1 playing a part in transcription activation. Gli2 works as both an activator and an inhibitor of transcription, but mostly as an activator. Transcription is inhibited by Gli3.[19]

The development of the nervous system, skeleton, limbs, lungs, heart, stomach, and embryo is all significantly influenced by this signaling pathway.

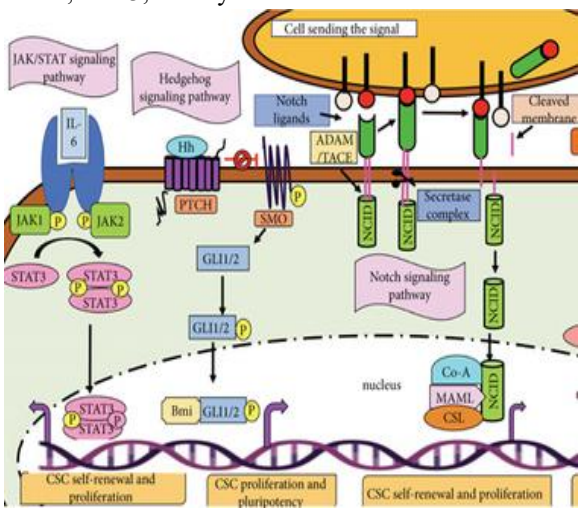
When the Hh ligand is not present, the target cell membrane's PTCH attaches to the SMO, inhibiting its function and eventually stopping the signaling [20]. By removing the inhibition of SMO, the spatial conformational change in the PTCH caused by the presence of the Hh ligand activates the transcription factor Gli. Gli controls cell growth, proliferation, and differentiation after translocating into the nucleus [21]

Through upregulating the expression of associated downstream markers of CSCs (e.g., ALDH1, Bmi-1, CCND1, CD44, C-MYC, Jagged1, Nanong, and Wnt2), Hh signaling can also promote the ability of CSCs to self-renew and spread. Certain suppressor genes and protooncogenes either directly or indirectly control Hh signaling in CSC migration and proliferation. The Sonic Hh effectors Gli1 and Gli2 are directly repressed in medulloblastoma stem cells by a transcriptional repressor, BCL6, and lymphoma oncoprotein. Because of its increased physical interaction with the β-catenin, Gli1 is degraded.MiR-122 specifically targets the Shh and Gli1 in lung CSCs. Therefore, it can be concluded that CSC growth, metastasis, and self-renewal depend on increased Hh signaling.[18]

- **JAK-STAT :**

The Janus kinase/signal transducers and activators of transcription (JAK-STAT) are stimulated by cytokines. Some cytokines and growth factors that are in charge of sending the signal along this pathway are interleukin 2-7, granulocytes/macrophage colony-stimulating factor, growth hormone, EGF, PDGF, and interferon. The JAK-STAT signaling system is involved in numerous essential biological processes, including immune control, cell proliferation, death, and differentiation. The three primary elements of this route are the transcription factor STAT, the tyrosine kinase JAK, and the tyrosine kinase-related receptor.

The cells have the tyrosine kinase JAK's binding site. To accomplish communications from the extracellular to the intracellular space, tyrosine residues of different target proteins are phosphorylated via JAK activation after binding with the ligands. While STAT has seven members in the family (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6) that are crucial for transcriptional activation and signal transduction, the JAK protein family consists of four members: JAK1, JAK2, JAK3, and Tyk2[22]



JAK catalyzes the tyrosine phosphorylation of the receptor by activating the tyrosine kinase-related receptor after receiving the signal from the upstream receptor molecule. The receptor molecule's phosphorylated tyrosine binds to the SH2 site of STAT and functions as a signal molecule. Tyrosine phosphorylation of STAT also takes place when it binds to the receptor, forming a dimer that enters the nucleus, influences the expression of the targeted genes and eventually causes the target cells to proliferate and differentiate[18]

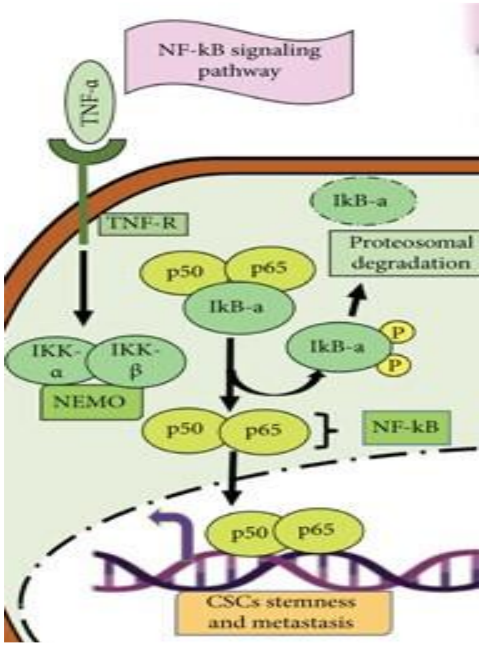
Numerous cancers exhibit aberrant and constitutive STAT3 activity as well as JAK2 mutations. Through the JAK1/STAT3 pathway, HIF-1α promotes the self-renewal of glioma stem-like cells [23]. IL-6 activates this pathway in ALDHhigh and CD126+ endometrial CSCs. In the case of breast CSCs, it also activates the downstream Oct4 gene, which transforms the nonstem cancer cells into cancer stem cells. Through the JAK1/STAT1

International Journal of Pharmaceutical research and Applications
Volume 10, Issue 4, Jul.-Aug. 2025, pp:529-536 www.ijprajournal.com ISSN: 2456-4494

pathway, AJUBA, a scaffold protein that is crucial for cell adhesion, differentiation, proliferation, and migration, also promotes the survival and proliferation of colorectal CSCs.

■ **NF-kB :**

The fast inducible transcription factor NF-κB is made up of five distinct proteins, primarily p65, RelB, c-Rel, NF-κB1, and NF-κB2 [24]. Its action is controlled by two main routes. Both the conventional and noncanonical NF-κB signaling pathways are among them. When the ligand (such as bacterial cell components, IL-1β, TNF-α, or lipopolysaccharides) attaches itself to the receptor (such as the Toll-like receptor, TNF receptor, IL-1 receptor, and antigen receptor), the canonical NF-κB pathways are activated. When these receptors are stimulated, IκB kinase (IKK protein) is further phosphorylated and activated. As illustrated in Figure 6, IKK1 proteins are also phosphorylated and activated in the noncanonical pathway by triggering the kinase (NIK), which in turn activates NF-κB. The phosphorylation of p100 is stimulated by the action of the IKK enzyme, which results in the creation of p52 [25].



Certain cytokines, proteases, and growth and angiogenesis-promoting substances are produced throughout the development and progression of tumors in order to activate the NF-κB signaling pathway. Overactivation of NF-κB signaling has been documented in numerous cancers . In the case of ovarian CSCs, CD44+ cells induce nuclear activation of the p50/RelA (p50/p65) dimer and increase the production of RelA, RelB, and IKKα, which in turn promotes self-renewal, metastasis, and CSC maintenance Therefore, it can be concluded that the increased NF-κB signaling plays a critical role in controlling CSC apoptosis, proliferation, and metastasis.

■ **NOTCH :**

Five structurally similar Notch ligands (Delta-like1, Delta-like3, Delta-like4, Jagged1, and Jagged2) and four Notch receptors (primarily Notch1, Notch2, Notch3, and Notch4) make up the highly conserved Notch signaling pathway. Certain physiological situations cause the delta ligand to connect to the Notch receptor, which in turn causes juxtacrine expression on nearby cells. The intracellular domain (ICD) of Notch is cleaved by two distinct enzymes, ADAM10 or TACE (TNF-α-converting enzyme, also called ADAM17), and a metalloprotease that catalyzes the S2 cleavage, thereby generating a substrate for the S3 cleavage through the γ-secretase complex.

Itis then translocated into the nucleus, where it binds to the transcription factor CSL, after mediating the release of NCID through proteolysis. The transcriptional activation complex NICD/CSL, which is formed as a result of this interaction, activates the BHLH transcription inhibitor family's targeted genes

Notch can function as an enzyme, oncogene, or tumor suppressor gene, depending on the surrounding conditions. Notch activation reduces apoptosis while promoting metastasis, self-renewal, and cell survival. Delta-like ligand 4 (DLL-4) is abundant in gastric CSCs, which stimulates tumor angiogenesis and metastasis . When MAP17 (DD96, PDZKIP1), a nonglycosylated membrane-associated protein found on the plasma membrane and Golgi apparatus, interacts with NUMB through the PDZ-binding domain in cervical CSCs, the Notch pathway is triggered. The Notch1 signaling is regulated by TACE/ADAM17. Inducible nitric oxide synthase, which supports CD24+/CD133+ liver cells' ability to self-renew, is what activates them [26].

TNF-α enhances the CSC-like phenotype in oral squamous cell carcinoma by activating Notch1 signaling. When there is no indication of hypoxia, Notch1 triggers the migration and invasion of ovarian CSCs . These recent investigations thus highlight the critical role that Notch signaling plays in CSC development, self-renewal, and metastasis.

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THERAPEUTIC STRATEGIES :

- **Target to Niche :**

Inflammatory cytokines, hypoxia, and the control of the perivascular niche's ability to promote self-renewal, proliferation, and differentiation are the primary characteristics of the CSC microenvironment. In tumors and stromal cells, a number of inflammatory cytokines (such as IL-1β, IL-6, and IL-8) are in charge of activating different pathways like STAT3 and NF-κB. Through the previously mentioned pathway, cytokine secretion promotes angiogenesis, metastasis, and self-renewal in a positive feedback loop. It has been noted that tumor growth is reduced when IL-6/IL-8 cytokine signaling is blocked.[27]

The stimulation of HIFs in a hypoxic milieu makes cells resistant to chemotherapy and radiation as well as cellular differentiation. Additionally, it controls apoptosis and angiogenesis. The Food and Drug Administration (FDA) has approved a few small compounds that function as HIF pathway inhibitors, including temsirolimus (CCI-779) for the treatment of renal cell carcinoma and bortezomib (Velcade®, PS-341) for the treatment of multiple myeloma in 2003. Other medications that prevent angiogenesis include bevacizumab (Avastin®), cediranib (AZD2171), sunitinib, and vandetanib. These medications work by preventing the vascular endothelial growth factor (VGEF), which is responsible for endothelial cell migration. Additionally, these medications impede CSCs' ability to self-renew, which prevents tumor growth and metastasis [28]

- **Targetting csc for Immunotherapy:**

By identifying cancer cells through the immune system, cancer immunotherapy primarily targets the growth and spread of cancer cells. Certain cell surface markers, including as ALDH, CD44, CD133, EpCAM, and HER2, that are expressed on CSCs are crucial for recognizing a specific antigen and identifying targets for CSC immunotherapies. The immune response is endogenously regulated by immunological checkpoints. Because they mediate coinhibitory signaling pathways, they also contribute to limiting autoimmunity. Programmed cell death-1 (PD1/PDL1) and CTL antigen 4 (CTLA-4/B7) are two examples of such immunoinhibitory pathways. It has been determined that these negative immune regulatory mechanisms shield cancer cells from immune cell death.[29]

- **Targetting CSC via Nanotechnology :**

By altering their surfaces to target CSCs, a variety of nanoparticles of various sizes can be readily created. These include carbon allotropes (such as carbon nanodiamond, graphene, and carbon nanotubes), noble metals (such as gold nanoparticles), organic polymers, and liposome nanoparticles. Graphene oxide (GO) is a graphene derivative containing carbon atoms bonded to oxygen functional groups, giving it extraordinary chemical flexibility. Consequently, graphene is a great vehicle for pharmaceuticals or nucleic acids for targeted cancer therapy since its surface may be readly altereid with a variety of biological compounds and agents of interest. By promoting differentiation and preventing proliferation, GO selectively targets a global phenotypic characteristic of CSCs and may decrease the quantity of true CSCs.[30]

II. CONCLUSION :

Cancer is among the illnesses that cause the most deaths globally. According to research done since the disease's first documented history, there are a number of reasons why people get cancer. Numerous elements, such as the environment, genetics, epigenetics, and certain medical conditions, make cancer inevitable. A closer look at the occurrence of cancer reveals the presence of cancer stem cells, also referred to as cancer-initiating factors. It's common knowledge that CSCs function similarly to normal somatic stem cells. They have characteristics including the ability to proliferate and replenish themselves. When it comes to cancer stem cells, traditional cancer therapy methods are useless.Chemotherapy is the standard treatment for many types of cancer. When cancer is present, chemotherapy .

Numerous signaling pathways and biomarkers are present in CSCs. As a result, not all of the regulatory elements that contribute to CSCs may be exploited as therapeutic targets. Finding realistic therapeutic targets that are exclusive to CSCs requires some innovative methods in order to target CSCs effectively without killing healthy cells. It is also important to take into account the elements that contribute to the stemness of CSCs. To effectively target CSCs, a number of problems still need to be addressed, including the investigation of tumor-specific traits of CSCs, the absence of models that accurately reflect the biological complexity of tumors, and difficulties in simulating the CSC-specific environment.

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International Journal of Pharmaceutical research and Applications
Volume 10, Issue 4, Jul.-Aug. 2025, pp:529-536 www.ijprajournal.com ISSN: 2456-4494

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