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Review

HERG1 and Cancer: Exploring the Nexus Between Ion Channels and Tumorigenesis

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ABSTRACT

The human ether-a-go-go-related gene-1 (HERG1) is a key structure involved in various physiological activities within voltage-gated potassium channels found in neurons, cardiac cells, and cancer cells, synthesizing a crucial potassium channel protein. Due to its role in potassium channels, HERG1 contributes to neurological network activities such as action potentials, polarization, depolarization, and functions in cardiac impulse conduction. Contrary to common belief, HERG1 plays a significant role in the molecular network of cancer. HERG1 accelerates carcinogenesis and tumorigenesis at abnormal expression levels, functioning as a biomarker. It is highly active in the molecular mechanisms of cancer and shows promise in targeted therapy research. Based on clinical findings, HERG1 directs researchers toward alternative therapeutic approaches. While combined treatment methods, incorporating traditional chemotherapy, may be employed, this will not be straightforward. Mapping out the complex network of molecular cancer biology and explaining the interactions between multiple signaling pathways will make the research process quite challenging and laborious. This review comprehensively evaluates HERG1's function in molecular cancer biology.

Keywords: Biology, cancer, HERG1, researchers, therapy.

The human ether-a-go-go-related gene-1 (HERG1) encodes a potassium channel protein that is essential in a variety of physiological functions. HERG1 is a voltage-dependent potassium channel found in various tissues and cell types, including the heart, neurons, and cancer cells.[1]

HERG1 has six α-helical transmembrane domains, with the N- and C-termini in the cytoplasm, a cyclic nucleotide-binding domain at the C-terminus, and a pore-forming area between segments S5 and S6.[2]

The HERG1 channels play a crucial role in regulating membrane excitability and action potential repolarization in cardiac myocytes, contributing to the heart's normal function.[1]

Abnormal HERG1 expression has been associated with various malignancies, such as esophageal squamous cell carcinoma, colorectal cancer, and glioblastoma multiforme.[3-5] In cancer cells, HERG1 expression is linked to processes like cell proliferation, invasion, and metastasis, suggesting its potential as a biomarker for tumor progression.[6,7]

Research has shown that HERG1 channels influence key processes in cancer cells, including cell proliferation, apoptosis, and migration, making them a potential target for anticancer therapy.[8] Elevated HERG1 expression has been correlated with poor prognosis in several malignancies, such as gastric cancer and esophageal squamous cell carcinoma.[9,10] Moreover, HERG1 overexpression in cancer cells has been linked to enhanced invasiveness and tumor growth, highlighting its critical role in cancer development and metastasis.[11]

TYPES OF TUMORS

A tumor, also known as a neoplasm, is an abnormal mass of tissue caused by uncontrolled cell growth that persists in the absence of the initial triggering stimuli. Tumors are classified as benign or malignant depending on their growth pattern, potential for invasion, and ability to metastasize.

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Benign Tumors

Benign tumors are defined as limited growths that do not infiltrate adjacent tissues or spread to distant locations. These tumors normally develop slowly and are often encapsulated, making them easier to surgically remove and less likely to reoccur.[12] Lipomas, which are benign tumors of adipose tissue, and fibromas, which develop from fibrous connective tissue, are two common instances. Despite their non-invasive nature, benign tumors can occasionally cause clinical problems due to their size or placement, perhaps squeezing adjacent tissues.[13]

Malign Tumors

Malignant tumors, or malignancies, are differentiated by their capacity to invade surrounding tissues and spread to distant organs, complicating therapy and prognosis.[14] These tumors are distinguished by their rapid and uncontrolled growth, high levels of cellular and nuclear atypia, and the ability to disrupt normal bodily systems. Genetic mutations have an important role in the etiology of malignant tumors by influencing essential regulatory mechanisms that control cell proliferation, apoptosis, and angiogenesis.[15] For example, mutations in the p53 tumor suppressor gene are widespread in many malignancies and contribute to uncontrolled cell proliferation and survival.[16]

Tumors are abnormal cell growths that can develop in a variety of tissues and organs throughout the body. They can be classed based on a variety of factors, including origin, behavior, and histological characteristics. Tumor classification is critical for appropriate diagnosis, prognosis, and treatment planning. The following are some frequent forms of tumors depending on their origin and characteristics:

Renal neoplasia: Renal neoplasms, namely renal cell carcinomas, are classified using the International Society of Urological Pathology Vancouver Classification. This categorization method distinguishes between several forms of renal tumors, including high-grade type 2 tumors and mixed groups of papillary renal cell carcinomas.[17]

Ovarian tumors: Ovarian tumors, particularly serous borderline tumors, are classified using developing concepts and diagnostic criteria. Serous borderline tumors have molecular and genetic similarities with low-grade serous carcinomas, emphasizing their borderline malignant potential.[18]

Brain tumors: Machine learning algorithms can classify brain tumors into multiple categories, such as primary gliomas and metastases, based on MRI texture and shape. This classification helps to distinguish between different forms of brain tumors and grade gliomas.[19]

Gastric cancer: Gastric tumors are classified using the TNM staging method, which provides information on tumor size, lymph node involvement, and metastasis. This classification system aids in identifying the prognosis and treatment options for stomach cancer.[20]

Soft tissue tumors: Adipocytic tumors, fibroblastic/myofibroblastic tumors, smooth muscle tumors, vascular tumors, and others are among the many types of soft tissue cancers. This classification system aids in detecting and classifying various types of soft tissue neoplasms.[21]

Pancreatic carsinomas: Pancreatic ductal adenocarcinomas are characterized according to molecular profiles and gene expression patterns. Molecular classifications such as Collisson's, Moffitt's, and Bailey's shed light on the biology and clinical aspects of pancreatic cancers.[22]

Central nervous system tumors: The central nervous system (CNS) tumors are classified based on molecular and practical approaches to tumor taxonomy. The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy aims to provide a comprehensive classification system for CNS tumors.[23]

The HERG1, which was initially discovered for its crucial role in cardiac electrophysiology, has now emerged as a key factor in oncogenesis, affecting tumor cell proliferation, apoptosis, invasion, and metastasis. This study aims to explain the molecular mechanisms that underpin HERG1's participation in cancer, investigate its potential as a biomarker for diagnosis and prognosis, and evaluate its feasibility as a therapeutic target.

BIOCHEMISTRY AND FUNCTION OF HERG1

Potassium ion channels have a critical function and importance for the repolarization process of the heart. HERG is a construct that codes for potassium ion channels. HERG1 is expressed in many tissues and cells, including tumor cells resulting from tumorigenesis, and forms heterotetramers.[24] Haplotyping at chromosome 7q36.1 has been associated with HERG1 defects and has been linked to schizophrenia.[25] The association of HERG1 molecules or channels with

integrin protein molecules in the conformational structure of integrin channels has been confirmed by scientific studies to play a role in downstream signaling and cancer progression.[26,27]

Conformationally, the HERG1 molecule has a tetrameric structure with a primary alpha subunit and an auxiliary beta subunit. A possible mutagenic condition in the HERG1 molecule leads to QT syndrome, which triggers ventricular arrhythmias and the risk of sudden cardiac death.[28] In addition, the functioning of HERG1 channels is potentially associated with carcinoma diseases and oral squamous diseases and is of prognostic importance.[29]

HERG1 modulates the formation of angiogenesis through the vascular endothelial growth factor (VEGF) signaling pathway in cancer molecular biology.[30] This modulation has been associated with endothelial proliferation, migration, and tube formation. Interaction of HERG1 with integrin protein molecules and chemokines leads to chemotherapy resistance in leukemia. Abnormal expression of HERG1 channels has been demonstrated in the malignant evolution of Barrett's esophagus.[31]

Overexpression of HERG1 Gene in Cancer Cells

The HERG1 gene overexpression has been extensively studied in a variety of human malignancies, where it plays an important role in cancer progression and malignancy. According to studies, the HERG1 protein is overexpressed in many cancers and has an important role in cellular processes such as proliferation, apoptosis, and invasion.[32] Overexpression of HERG1 channels has been associated with cancer cell transformation and proliferation, indicating that it may play a function as an oncogene in cancer development. HERG1 channels have been linked to the advancement of numerous forms of cancer, such as pancreatic cancer, gastric cancer, bladder cancer, and ovarian cancer, demonstrating the widespread presence of HERG1 overexpression in cancer.[3]

Molecular Mechanisms of HERG1 on Cancer Development

The molecular mechanism of cancer has a wide range. Many studies are being conducted by research scientists to elucidate the molecular biology of cancer. The genetic complications contained in the HERG1 gene have been found to be associated in the molecular biology of cancer. The cell cycle directly regulates the morphology, physiology and even biochemical structures of the cell. Here, many molecular cellular structures cooperate. HERG1 is directly involved in the regulation of the cell cycle. To exemplify this relationship with another study, as a result of HERG1 stimulation, cyclin E2, one of the important cell cycle regulators, will decrease in level. This decrease will activate the cell cycle in breast cancer cells and cause an increase. In this way, HERG1 indirectly accelerates the cell cycle reactions of carcinogenesis structures by accelerating the tumorigenesis process. Another critical example is that suppressing the HERG1 gene present in pancreatic cells blocks the G1 phase in the cell cycle.[33]

Cancer cells are known to be invasive. HERG1 can be linked to this invasive state. It promotes metastasis, one of the secondary phases of invasive cancer biology. HERG1 gene expression has been associated with the invasiveness of colorectal cancer cells and as a result, colorectal cancer cells tend to metastasize. It has also been reported to be associated with advanced disease and metastasis in head and neck squamous cell carcinomas. Activation of integrin, a cell membrane protein, promotes the production and translocation of HERG1 to the plasma membrane. From a molecular perspective, the association of the channel with integrins seems to increase its carcinogenic potential, as it has been shown to increase signaling capacity in cancer cells.[34]

Within the scope of the molecular mechanism of HERG1, invasion, metastasis, regulation, and proliferation have been mentioned so far, but HERG1 has also been associated with apoptosis, i.e. programmed cell death mechanism in cancer biology. The stimulation, activation, and regulation of HERG1 is important for cisplatin-induced apoptosis in gastric cancer cells. Cisplatin is a type of chemotherapy drug, which may lead to a different treatment modality in terms of chemoresistance.[35]

HERG1 and Cancer Development: Signaling Pathways

Signaling pathways act as servants for the functioning of the cell. Cells' need for transport, communication, biochemical regulations, and many other functions are realized through signaling pathways. There is no doubt that carcinogenic cells involved in the formation of carcinogenesis, morphological, physiological, and biological phenomena of the tumor in the formation of the tumor are the work of signaling pathways. Signaling pathways are molecularly complex but functionally simple: to maintain homeostasis. The slightest disconnection, loss of function, or any abnormal

condition in signaling pathways disrupts the internal balance. HERG1 is known to use signaling pathways in cancer development. Epidermal growth factor receptor (EGFR) interacts with HERG1. In Pancreatic ductal adenocarcinoma, HERG1 interacts with EGFR to increase the signaling of the receptor and has been found to promote cell proliferation and migration. In addition, the Mitogen-activated protein kinases (MAPK) molecule has various functions in the mitochondria organelle. MAPK regulates increased cell and cell survival. HERG1 integrins, especially β1 integrin, have been linked to increased inflammation and aggressive behavior in various cells. HERG1 and integrins play an important role in focal adhesion kinase activation in the immune system.[36-38]

Apart from EGFR, HERG1 has also been associated with the PI3K/AKT signaling pathway, which regulates cellular events such as cell survival and proliferation in cell signaling. As a result of stimulation and activation of HERG1, the molecule promotes the functioning of PI3K/AKT. In Esophageal squamous cell carcinoma (ESCC), after this stimulation, it both accelerates and increases the synthesis of the TXNDC5 protein molecule, which plays a role in cancer progression. Here, it is understood that HERG1 is effective and functional in carcinogenesis and tumorigenesis. This may result in cell proliferation and resistance to apoptosis.[3,32]

Role and Effects of HERG1 in the Metastasis Process

When we look at the molecular biology of cancer, we are confronted with a very complex series of cellular events. Cancer formation and tumor formation together with cancer formation are composed of many molecular processes. These processes are long and consist of phases. On the contrary, the same is true for cancer formation. The primary stage of cancer is less invasive than the secondary stage, healthier in terms of prognosis, less peripheral, more localized, and composed of benign cells. This condition is not permanent, as it can be transformed into the secondary stage. The most characteristic feature of the secondary stage is undoubtedly the mechanism of metastasis. Metastasis is the process of moving the cancer to different regions by creating different pathways from the region where it is located or formed. Metastasis is quite peripheral. Metastatic cancers are very difficult to treat even if traditional treatment methods are used. HERG1 promotes metastasis. The mechanisms it contributes to include epithelial-mesenchymal transition (EMT), modulation of signaling pathways, and other cellular components. One of the critical processes in metastasis is EMT, which enables cancer cells to promote the ability to migrate. Within the scope of their studies, research scientists have shown that HERG1 levels are closely associated with ESCC EMT markers. In particular, changes in HERG1 expression can significantly affect the expression of important EMT markers and thus increase the invasive potential of cancer cells. This association underscores the importance of HERG1 in facilitating the transition of cancer cells from a quiescent phenotype to a migratory phenotype, a crucial step in the metastatic cascade.[3]

HERG1 and Cancer Prognosis: Clinical Findings

The HERG1 potassium channel, also referred to as KCNH2 has been identified as a significant biomarker in various malignancies, influencing both tumor progression and prognosis. Clinical studies demonstrate that HERG1 expression correlates with advanced disease stages and poor clinical outcomes across several cancer types, including head and neck squamous cell carcinoma, pancreatic ductal adenocarcinoma, and colorectal cancer. Increased HERG1 expression in head and neck squamous cell carcinoma is linked to lymph node metastases, advanced disease stages, and lower disease-specific survival. This tendency is mirrored in pancreatic ductal adenocarcinoma, where HERG1 channels are thought to drive tumor malignancy and may serve as a prognostic marker, especially in identifying high-risk patient subgroups. HERG1 has been demonstrated to increase esophageal squamous cell carcinoma development and metastasis by activating the PI3K/AKT pathway, showing that it functions as an oncogene in this context.[3,39]

Cancer markers have been a highly researched and studied area for developing treatment strategies. The current prognostic implications of HERG1, when considered in conjunction with its expression on Glut-1, extend to colorectal cancer, where it is associated with patients with stage I and II disease.[40] In a study of gastric dysplasia, HERG1 was identified as a potential biomarker for cancer progression and found suitable for use within clinical surveillance protocols.[41]

HERG1 and Treatment Strategies: Drug Development and Targeted Therapies

Up to this point, the roles and effects of the HERG1 potassium channel (KCNH2) in cancer and tumor biology have been discussed. In addition to conventional treatment methods, various strategies, pathways, or targeted therapies are being developed

for HERG1. One intriguing technique involves using anti-HERG1 antibodies and their derivatives, such as single-chain variable fragments, combined with cytotoxic drugs to selectively target cancer cells expressing HERG1. This approach aims to deliver drugs directly to tumor cells, minimizing off-target effects and malformations while protecting healthy tissues, thus improving treatment efficacy. Targeting specific conformations of HERG1 channels may provide a more refined approach to limiting their function in cancer cells, potentially reducing tumor growth and metastasis. Blockade of HERG1 expression has been shown to reduce cell proliferation in various cancer types, including small-cell lung cancer. Application of HERG1-targeting siRNA has demonstrated significant tumor growth inhibition in preclinical models. Modulation of HERG1 activity has also been linked to the regulation of angiogenesis, suggesting that HERG1 inhibitors may normalize tumor vasculature and enhance the efficacy of existing treatments, such as anti-VEGF therapies. Recent studies have also highlighted the potential of combining HERG1-targeted therapies with conventional chemotherapeutics. A bispecific antibody targeting the HERG1/β1 integrin complex has shown promise when used alongside gemcitabine in pancreatic ductal adenocarcinoma, indicating a synergistic effect that could improve patient outcomes. It has been proposed that combining HERG1 blockers with standard chemotherapy could overcome drug resistance in colorectal cancer by enhancing the pro-apoptotic effects of drugs like cisplatin.[42-49]

In conclusion, HERG1 and its associated potassium channels play highly effective roles in the molecular biology of cancer and tumor biology. They are involved in cellular and biochemical activities such as cancer cell progression, proliferation, secretion, invasion, metastatic characteristics, and apoptosis. Overexpression of HERG1 has been observed in malignancies associated with colorectal cancer, pancreatic cancer, head and neck cancers, and lung cancers. While HERG1 functions as a molecular biomarker in these malignancies, it is also crucial as a target for therapeutic interventions. Mapping out its complex molecular mechanisms, particularly its interactions with signaling pathways such as PI3K/AKT and its association with integrins provides new methodologies for developing targeted therapies. Chemotherapy, one of the conventional cancer treatments, can be combined with various HERG1 inhibitors. For instance, when combined with siRNA and bispecific antibodies, it has the potential to improve therapeutic efficacy and overcome drug resistance. Such combined treatment approaches can result in an increase in pro-apoptotic effects while minimizing off-target effects and reducing toxicity or cytotoxicity. In light of these findings, future research should aim to define the precise functions of HERG1 in various cancer types, optimize HERG1-targeted drugs, and explore their therapeutic applications. Considering the significant preclinical data, translating HERG1-based drugs into clinical practice holds the potential to offer new, more effective therapeutic alternatives for cancer patients, improve outcomes, and address the limitations of current treatment approaches.

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