Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/29/20240631

Maternal embryonic leucine zipper kinase in cancer progress and therapeutic potentials

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Abstract. This review delves into the investigation of Maternal Embryonic Leucine Zipper Kinase (MELK) and its significance in different cancer types. The primary emphasis is placed on understanding its role in cancer cell proliferation, migration, invasion, and resistance to therapeutic interventions. The intricate mechanisms of action exhibited by MELK are of significant importance in the context of cancer progression. These mechanisms encompass a wide range of biological processes, including gene regulation, cellular activities, and interactions at the tissue level. This highlights the multifaceted nature of MELK's involvement in cancer development and underscores its significance in this context. This essay explores the potential of MELK as a diagnostic and prognostic biomarker, with a focus on its altered expression patterns in various cancer types. Furthermore, this study delves into the investigation of MELK as a highly promising target for cancer therapy. It provides an in-depth analysis of the progress made in the development of MELK inhibitors and explores their potential clinical applications. The research endeavours in this study focus on addressing challenges related to therapeutic resistance and biomarker validation. Additionally, the investigation explores potential opportunities for combination therapies and personalised medicine approaches. The future directions of research on maternal embryonic leucine zipper kinase (MELK) encompass an in-depth investigation into its underlying molecular mechanisms, the validation of clinical biomarkers associated with MELK, and the exploration of effective combination strategies involving MELK. The role of MELK in cancer and the possibility to utilize it as a target for therapy have garnered significant attention due to their potential to advance precision cancer care and improve patient outcomes.

Keywords: MELK, Cancer progression, Combination Therapy, Precision Medicine.

1. Introduction

MELK is a protein kinase that has been linked to the progress of numerous cancer types. Several varieties of cancer, including breast, prostate, lung, ovarian, and liver cancers, have been observed to have elevated expression levels of the MELK gene. This overexpression of MELK has been found to be correlated with unfavourable prognosis and decreased overall survival rates in affected individuals [1]. The research findings indicate that MELK has demonstrated the ability to enhance various cancer cell processes, including proliferation, migration, invasion, and resistance to therapeutic interventions. Additionally, MELK has been observed to influence the tumour microenvironment, thereby facilitating

DOI: 10.54254/2753-8818/29/20240631

tumour growth and evading immune surveillance [2]. Therefore, targeting MELK could be a promising therapeutic strategy for cancer treatment.

2. Briefing of MELK in cancer progress

MELK has garnered considerable attention in the field of cancer research due to its demonstrated involvement in the development and advancement of diverse cancer types. The mechanisms through which MELK promotes cancer are complex and involve gene, cell, and tissue-level changes.

At the gene level, MELK expression can be regulated by several transcription factors, including E2F1, a transcription factor that promotes cell cycle progression and DNA synthesis [3]. According to previous research findings, it has been observed the overexpression of MELK in breast cancer cells when exposed to E2F1, a transcription factor. These studies provide evidence for a potential regulatory relationship between E2F1 and MELK in the context of breast cancer. Additionally, it is important to acknowledge that MELK possesses the capacity to activate diverse downstream effects. PI3K/AKT and MAPK/ERK pathways are mostly investigated, whose signaling cascades in promoting the proliferation and survival of cancer cells has been widely recognized [4].

At the cellular level, MELK has a crucial role in the regulation of several important cellular processes. These processes include the progression of cell cycle, apoptosis, and response to DNA damage [5].

Based on prior research, it has been determined that MELK exerts a substantial influence on the promotion of cancer cell proliferation. This is accomplished through its capacity to regulate the gene transcription which are implicated in the progression of the cell cycle, particularly those associated with the transition from the G1 to S phase [6]. Furthermore, it has been discovered that the protein MELK has the capacity to inhibit apoptosis by exerting regulatory control on the expression of anti-apoptotic proteins [7]. The suppression of MELK has demonstrated the ability to enhance programmed cell death in cancer cells and lower the progression of tumor both in vitro and in vivo.

At the tissue level, it has been observed that MELK is also relate to the facilitation of cancer cell migration and invasion. The regulation of matrix metalloproteinases (MMPs) plays an essential role in facilitating tumour invasion by breaking down the extracellular matrix [8].

The modulation of the tumour microenvironment by MELK has been observed to involve the regulation of cytokines and chemokines expression. These molecules play a crucial role in promoting angiogenesis, the formation of new blood vessels, and immune suppression [9]. Previous studies have demonstrated that the inhibition of MELK leads to a decrease in tumour cell invasion and angiogenesis both in vitro and in vivo [10].

The expression of MELK is commonly found in various types of cancer, including breast, lung, prostate, and pancreatic cancer. The close association between the expression of MELK and the progression of cancer, unfavourable prognosis, and the emergence of resistance to therapeutic interventions has been observed in these specific types of cancers. Previous studies have demonstrated that MELK, also referred to as maternal embryonic leucine zipper kinase, exhibits the capacity to confer resistance against a range of chemotherapy drugs, including paclitaxel and doxorubicin. Resistance to cancer treatment is a complex phenomenon that involves various mechanisms. One such mechanism is the promotion of cancer cell survival, which allows the cancer cells to continue proliferating despite the presence of treatment. Additionally, another mechanism involved in resistance is the inhibition of apoptosis, a natural process of programmed cell death. Apoptosis plays a crucial role in eliminating damaged or abnormal cells, including cancer cells. However, when apoptosis is inhibited, cancer cells can evade cell death and persist, contributing to treatment resistance [11]. The research findings indicate that the inhibition of MELK has demonstrated the potential to augment the effectiveness of chemotherapy drugs both in vitro and in vivo.

Currently, there is no specific diagnostic test available for MELK cancer. However, MELK expression can be detected using various methods as listed below [12].

IHC involves the use of antibodies that bind to MELK protein in tissue samples, allowing the visualization and quantification of MELK expression levels in cancer cells. IHC can be performed on biopsy or surgical specimens and is a routine diagnostic test used in clinical pathology [13].

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qPCR is a molecular biology technique that quantifies the amount of MELK RNA in cancer cells. qPCR can be performed on biopsy or blood samples and provides a quantitative measure of MELK expression levels.

In addition to detecting MELK expression, other diagnostic tests may be used to determine the extent of cancer and its prognosis. Various imaging modalities, such as computed tomography (CT) scans, magnetic resonance imaging (MRI), and positron emission tomography (PET) scans, are commonly used in this context [14].

3. Function and expression of MELK in cancer

3.1. MELK in cell proliferation, migration, invasion, and treatment resistance

MELK in promoting various aspects of cell behaviour, such as proliferation, migration, invasion, and therapy resistance, has been extensively studied in mammalian cells [1]. The mechanisms of MELK's action encompasses a multitude of signalling pathways and cellular processes.

Promoting cell proliferation through the regulation of cell cycle progression has been well-documented in scientific literature. The upregulation of cyclin D1 and CDK4, has been observed as a consequence of the overexpression of MELK [6]. The protein MELK has been found to play a role in phosphorylating and subsequently inactivating the tumour suppressor protein p53. This interaction has been shown to lead to a decrease in cell cycle arrest and apoptosis [15].

Its function in cancer cell migration and invasion has been extensively studied, revealing its regulatory influence on the expression of genes associated with cell adhesion and extracellular matrix degradation. The overexpression of MELK has been observed to result in an upregulation of MMPs, specifically matrix metalloproteinases. These enzymes play a crucial role in the degradation of the extracellular matrix, thereby facilitating the invasion of cancer cells. MELK also enhances the expression of integrin α6β1, which is involved in cell adhesion and migration [16].

MELK has been shown to promote resistance to chemotherapy and radiation therapy by inhibiting apoptosis and promoting DNA repair. MELK overexpression decreases the reactivity of cancer cells to chemotherapy drugs like paclitaxel and doxorubicin. MELK also promotes DNA repair by phosphorylating and activating the DNA repair protein BRCA2, which can lead to increased resistance to DNA damage caused by chemotherapy and radiation therapy [17].

In addition to these mechanisms, MELK has been shown to modulate the tumor microenvironment by promoting angiogenesis and immune suppression. The overexpression of MELK has been observed to result in an upregulation of VEGF, a key factor involved in the process of angiogenesis and the subsequent growth of tumours. MELK also inhibits the activation and proliferation of T-cells, which are important immune cells that can recognize and eliminate cancer cells [18].

The overexpression of MELK has been detected in multiple types of cancer, suggesting its potential role as an oncogene. The association between MELK expression and cancer progression has been studied extensively across different cancer types.

3.2. MELK expression in various types of cancer

Breast Cancer: MELK has been detected in breast cancer, with a particular emphasis on its presence in aggressive subtypes such as triple-negative breast cancer (TNBC). According to previous studies, it has been observed that there is a correlation between elevated MELK expression in triple-negative breast cancer (TNBC) and certain unfavourable outcomes. These outcomes include an increase in tumour growth, resistance to chemotherapy, and poorer patient outcomes [11]. The presence of this particular factor in breast cancer stem cells indicates its potential role in the initiation and recurrence of cancer.

Ovarian Cancer: High-grade serous carcinoma, a common and aggressive subtype has overexpressed MELK profile [19]. The expression of MELK has been observed to be dramatically elevated in various malignancies. This heightened expression has been found to be correlated with unfavourable prognostic outcomes, including increased tumour growth and resistance to chemotherapy. The potential

DOI: 10.54254/2753-8818/29/20240631

involvement of a specific factor in the control of cancer stem cell populations within ovarian tumours has been suggested.

Glioblastoma multiforme: MELK's role in maintaining GBM stem-like cells suggests a contribution to tumor aggressiveness and resistance to treatment [20].

The relationship between MELK and cancer progression is complex and varies among different cancer types. MELK's role in promoting cell proliferation, survival, and stemness pathways indicates its potential as a therapeutic target. Inhibiting MELK could potentially reduce tumor growth, sensitize cancer cells to therapies, and disrupt cancer stem cell populations. Ongoing clinical trials are currently being conducted to evaluate the effectiveness of MELK inhibitors as innovative therapeutic approaches. Nevertheless, it is vital to note that although MELK exhibits promising characteristics, additional investigation is warranted in order to comprehensively comprehend its underlying mechanisms, ascertain its functional significance, and evaluate its potential advantages for individuals afflicted with cancer.

4. MELK clinical relevance

4.1. Potential of MELK as a Biomarker for Cancer Diagnosis and Prognosis

The investigation of modified expression patterns of MELK (Maternal Embryonic Leucine Zipper Kinase) across various cancer types has garnered considerable interest as a prospective biomarker for the detection and prediction of cancer. The examination of MELK expression has produced noteworthy discoveries concerning its capacity to provide valuable insights into the aggressiveness of various diseases. Consequently, it has emerged as a promising tool that can effectively guide treatment decisions.

Multiple types of cancer, including breast, ovarian, liver, and lung cancers, have been discovered to have elevated MELK expression. The detection of MELK expression levels has the potential to aid in the early detection of cancer, leading to more timely intervention and improved patient outcomes.

MELK expression has been observed to correlate with a poor prognosis in a variety of cancer types. It has been observed in previous studies that patients with elevated levels of MELK expression tend to experience unfavourable outcomes. These outcomes include a lower overall survival rate and a higher probability of disease recurrence [19]. Assessing MELK expression in tumour tissues could aid physicians in identifying high-risk patients and customising treatment plans. MELK expression may function as a biomarker for predicting treatment response. Cancers with elevated MELK expression may be more resistant to certain therapies, and patients may benefit from individualised treatment strategies that take MELK expression status into account.

4.2. Potential of MELK as a Target for Cancer Therapy

The overexpression of MELK in various cancer types, along with its role in promoting tumor growth and survival, has positioned it as a potential therapeutic target. Developing drugs that inhibit MELK's activity could offer a novel approach to cancer treatment.

Targeted Therapy: Targeted therapy is an approach in cancer treatment that focuses on specifically targeting the underlying molecular alterations driving the growth and survival of cancer cells. Unlike conventional chemotherapy, which affects both healthy and cancerous cells, targeted therapies aim to selectively interfere with the unique molecular pathways that are dysregulated in cancer cells. MELK inhibitors are being investigated as targeted therapies. By using target therapy, MELK inhibitors aim to disrupt cancer cell proliferation, survival pathways, and stemness, making them particularly relevant in aggressive and therapy-resistant cancers. They work by inhibiting MELK's kinase activity, interrupting cell cycle progression, promoting apoptosis, and potentially targeting therapy-resistant cancer stem cells.

Combination Therapy: Combination therapy, the practice of using multiple treatments concurrently, is an approach in cancer treatment that aims to enhance therapeutic outcomes by targeting different aspects of the disease simultaneously [21]. MELK inhibitors could be used in combination with existing therapies, such as chemotherapy or targeted treatments, multiple aspects of cancer can be targeted. This approach addresses therapy resistance mechanisms, potentially yielding synergistic effects and

DOI: 10.54254/2753-8818/29/20240631

overcoming challenges posed by high MELK expression in aggressive cancers, might improve patient outcomes.

Precision Medicine: Precision medicine, alternatively referred to as personalised medicine, is a field of study that endeavours to customise medical interventions and therapies based on the distinctive attributes of individual patients. This approach takes into account the distinct genetic and molecular composition of a patient's ailment, with the goal of optimising medical decisions and treatments to suit their specific needs. MELK-targeted therapies could potentially be part of a precision medicine approach, where treatment decisions are based on the molecular characteristics of individual tumors. Assessing MELK expression levels could guide the selection of patients who are most likely to benefit from these therapies.

Clinical Trials: Ongoing clinical trials are being conducted to evaluate the safety and efficacy of MELK inhibitors across various cancer types. The primary purpose of these trials is to evaluate the therapeutic potential of inhibiting MELK (Maternal Embryonic Leucine Zipper Kinase) and its effect on patient outcomes.

5. Prospectives

Research on MELK continues to evolve, driven by the increasing recognition of its significance in cancer biology. Several key areas of investigation hold promise for advancing our understanding of MELK's role in cancer and its potential as a therapeutic target:

Elucidating Molecular Mechanisms: Elucidating Molecular Mechanisms is the process of clarifying and understanding the intricate biochemical and cellular pathways that are regulated by a particular molecule, such as MELK in this context. In the case of MELK, it involves uncovering how this kinase enzyme influences various cellular processes and signaling pathways within a cell. It informs the development of targeted treatments that can disrupt MELK's oncogenic functions and improve the efficacy of cancer therapies.

Clinical Biomarker Validation: Validating MELK expression levels as reliable biomarkers in larger clinical cohorts is crucial. Establishing the correlation between MELK expression and patient outcomes will solidify its role as a predictive marker for patient selection, prognosis, and treatment response. This validation is essential for implementing MELK inhibitors as a precision medicine approach in clinical practice.

Combination Strategies: Investigating effective combinations of MELK inhibitors with other therapies, such as immunotherapies or existing targeted agents, holds significant promise. Combining MELK inhibitors with complementary treatments could enhance their effectiveness, overcome resistance mechanisms, and broaden their applicability across various cancer types and contexts. Well-designed studies exploring synergistic effects and optimal dosing are vital for maximizing therapeutic benefits.

6. Conclusion

In conclusion, MELK has emerged as a significant player in cancer biology, with its overexpression implicated in various cancer types. Its involvement in promoting cancer cell proliferation, migration, invasion, and therapy resistance underscores its potential as a therapeutic target. The intricate mechanisms through which MELK operates, from gene regulation to cellular processes, highlight its complexity and importance in cancer progression.

The clinical implications of MELK are substantial. The potential of this biomarker in the field of cancer diagnosis, prognosis, and treatment response has garnered significant attention, highlighting its importance in informing personalised treatment approaches.

Furthermore, the development of MELK inhibitors as targeted therapies offers new avenues for improving patient outcomes. However, challenges such as therapeutic resistance, clinical translation, and biomarker validation must be addressed to fully realize the potential of MELK-targeted therapies.

Future research should focus on unraveling MELK's molecular mechanisms, validating its role as a clinical biomarker, and exploring effective combination strategies. By advancing our understanding of

DOI: 10.54254/2753-8818/29/20240631

MELK's intricate role in cancer and harnessing its therapeutic potential, we move closer to developing more precise and effective treatments that could revolutionize cancer care. As MELK research continues to evolve, it holds promise for transforming the landscape of cancer therapy and improving the lives of patients worldwide.

References

[1] R. Ganguly, A. Mohyeldin, J. Thiel, H.I. Kornblum, M. Beullens, I. Nakano, MELK—a conserved kinase: functions, signaling, cancer, and controversy, Clinical and translational medicine 4 (2015) 1-8.

[2] P. Mondal, B. Kaur, J. Natesh, S.M. Meeran, The emerging role of miRNA in the perturbation of tumor immune microenvironment in chemoresistance: Therapeutic implications, Seminars in cell & developmental biology, Elsevier, 2022, pp. 99-113.

[3] H. Sun, H. Ma, H. Zhang, M. Ji, Up-regulation of MELK by E2F1 promotes the proliferation in cervical cancer cells, International Journal of Biological Sciences 17(14) (2021) 3875.

[4] Q. Zhang, C. Zhong, J. Shen, S. Chen, Y. Jia, S. Duan, Emerging role of LINC00461 in cancer, Biomedicine & Pharmacotherapy 152 (2022) 113239.

[5] L. Beke, C. Kig, J.T. Linders, S. Boens, A. Boeckx, E. van Heerde, M. Parade, A. De Bondt, I. Van den Wyngaert, T. Bashir, MELK-T1, a small-molecule inhibitor of protein kinase MELK, decreases DNA-damage tolerance in proliferating cancer cells, Bioscience reports 35(6) (2015) e00267.

[6] S. Chen, Q. Zhou, Z. Guo, Y. Wang, L. Wang, X. Liu, M. Lu, L. Ju, Y. Xiao, X. Wang, Inhibition of MELK produces potential anti‐tumour effects in bladder cancer by inducing G1/S cell cycle arrest via the ATM/CHK2/p53 pathway, Journal of Cellular and Molecular Medicine 24(2) (2020) 1804-1821.

[7] R. Edupuganti, J.M. Taliaferro, Q. Wang, X. Xie, E.J. Cho, F. Vidhu, P. Ren, E.V. Anslyn, C. Bartholomeusz, K.N. Dalby, Discovery of a potent inhibitor of MELK that inhibits expression of the anti-apoptotic protein Mcl-1 and TNBC cell growth, Bioorganic & medicinal chemistry 25(9) (2017) 2609-2616.

[8] S. Crispi, R.A. Calogero, M. Santini, P. Mellone, B. Vincenzi, G. Citro, G. Vicidomini, S. Fasano, R. Meccariello, G. Cobellis, Global gene expression profiling of human pleural mesotheliomas: identification of matrix metalloproteinase 14 (MMP-14) as potential tumour target, PLoS One 4(9) (2009) e7016.

[9] Z. Zhang, C. Sun, C. Li, X. Jiao, B.B. Griffin, S. Dongol, H. Wu, C. Zhang, W. Cao, R. Dong, Upregulated MELK leads to doxorubicin chemoresistance and M2 macrophage polarization via the miR-34a/JAK2/STAT3 pathway in uterine leiomyosarcoma, Frontiers in oncology 10 (2020) 453.

[10] R.B. Craveiro, M. Ehrhardt, M.I. Holst, T. Pietsch, D. Dilloo, In comparative analysis of multi-kinase inhibitors for targeted medulloblastoma therapy pazopanib exhibits promising in vitro and in vivo efficacy, Oncotarget 5(16) (2014) 7149.

[11] M.K. Pitner, J.M. Taliaferro, K.N. Dalby, C. Bartholomeusz, MELK: a potential novel therapeutic target for TNBC and other aggressive malignancies, Expert Opinion on Therapeutic Targets 21(9) (2017) 849-859.

[12] Y. Zhao, T. Du, L. Du, P. Li, J. Li, W. Duan, Y. Wang, C. Wang, Long noncoding RNA LINC02418 regulates MELK expression by acting as a ceRNA and may serve as a diagnostic marker for colorectal cancer, Cell death & disease 10(8) (2019) 568.

[13] R. Kuner, M. Fälth, N.C. Pressinotti, J.C. Brase, S.B. Puig, J. Metzger, S. Gade, G. Schäfer, G. Bartsch, E. Steiner, The maternal embryonic leucine zipper kinase (MELK) is upregulated in high-grade prostate cancer, Journal of molecular medicine 91 (2013) 237-248.

[14] F. Hu, C. Gong, Y. Gai, D. Jiang, Q. Liu, S. Wang, M. Hu, R. Pi, H. Shu, J. Hu, [18F] F-ET-OTSSP167 Targets Maternal Embryo Leucine Zipper Kinase for PET Imaging of Triple-Negative Breast Cancer, Molecular Pharmaceutics 18(9) (2021) 3544-3552.

DOI: 10.54254/2753-8818/29/20240631

[15] C. Gu, Y.K. Banasavadi-Siddegowda, K. Joshi, Y. Nakamura, H. Kurt, S. Gupta, I. Nakano, Tumor-specific activation of the C-JUN/MELK pathway regulates glioma stem cell growth in a p53-dependent manner, Stem cells 31(5) (2013) 870-881.

[16] M. Kanda, Y. Kodera, Molecular mechanisms of peritoneal dissemination in gastric cancer, World journal of gastroenterology 22(30) (2016) 6829.

[17] C. Speers, S.G. Zhao, V. Kothari, A. Santola, M. Liu, K. Wilder-Romans, J. Evans, N. Batra, H. Bartelink, D.F. Hayes, Maternal embryonic leucine zipper kinase (MELK) as a novel mediator and biomarker of radioresistance in human breast cancer, Clinical Cancer Research 22(23) (2016) 5864-5875.

[18] B. Li, J. Yan, T. Phyu, S. Fan, T.-H. Chung, N. Mustafa, B. Lin, L. Wang, P.J.A. Eichhorn, B.-C. Goh, MELK mediates the stability of EZH2 through site-specific phosphorylation in extranodal natural killer/T-cell lymphoma, Blood, The Journal of the American Society of Hematology 134(23) (2019) 2046-2058.

[19] R.S. Kohler, H. Kettelhack, A.M. Knipprath-Mészaros, A. Fedier, A. Schoetzau, F. Jacob, V. Heinzelmann-Schwarz, MELK expression in ovarian cancer correlates with poor outcome and its inhibition by OTSSP167 abrogates proliferation and viability of ovarian cancer cells, Gynecologic oncology 145(1) (2017) 159-166.

[20] X. Zhang, J. Wang, Y. Wang, G. Liu, H. Li, J. Yu, R. Wu, J. Liang, R. Yu, X. Liu, MELK inhibition effectively suppresses growth of glioblastoma and cancer stem-like cells by blocking AKT and FOXM1 pathways, Frontiers in Oncology 10 (2021) 608082.

[21] R.B. Mokhtari, T.S. Homayouni, N. Baluch, E. Morgatskaya, S. Kumar, B. Das, H. Yeger, Combination therapy in combating cancer, Oncotarget 8(23) (2017) 38022.