Therapeutic Potential of Targeting Epigenetic Factors HIF-1α and KDM3A in Ovarian Cancer and PCOS

Aashritha Ramesh[1] and Dr. Swati Shah[#]

[1]SRM Institute of Science and Technology, India
[#]Advisor

ABSTRACT

Ovarian cancer and polycystic ovary syndrome (PCOS) are significant health concerns for women, posing challenges in terms of treatment and prognosis. Hypoxia-inducible factor 1 alpha (HIF-1α) and lysine demethylase 3A (KDM3A) have emerged as promising therapeutic targets for both conditions due to their involvement in critical cellular processes. This article explores the therapeutic potential of targeting HIF-1α and KDM3A in ovarian cancer and PCOS, investigating their molecular mechanisms in disease progression, including angiogenesis, cell proliferation, and metabolic dysregulation. Recent preclinical and clinical studies evaluating the effectiveness of HIF-1α and KDM3A inhibitors are discussed, emphasizing their potential as innovative therapeutic strategies. These findings highlight the importance of understanding the complex interplay between HIF-1α, KDM3A, and the pathogenesis of ovarian cancer and PCOS, ultimately facilitating the development of targeted therapies.

Introduction

Ovarian Cancer

Ovarian Cancer is a highly fatal gynecological tumor. It is the fifth-most leading cause of cancer related deaths in women all over the world. The incidence of ovarian cancer varies in different parts of the world but has the highest rate of occurrence in developed countries (Siegel et al., 2020). Most of the cases of ovarian cancer are diagnosed at an advanced stage which makes this disease extremely lethal.

Ovarian cancer is a heterogenous disease that can be categorized on the basis of histological and molecular characterizations into various subtypes (Kurman & Shih, 2016). Histologically, the most common subtype of ovarian cancer is high-grade ovarian serous carcinoma which is 70% of the total number of ovarian cancer cases (Bowtell et al., 2015). Other histological classifications of ovarian cancer include endometrioid, clear cell, mucous, and low-grade serous carcinoma.

There are numerous factors that are associated with the risk of ovarian cancer occurrence- age, a family history of ovarian cancer, endometriosis, and mutations in the BRCA1/2 genes(Menon et al., 2018). The reason why most cases of ovarian cancer are detected at an advanced stage is because the early stages are often asymptomatic, which makes it hard for any kind of tumor detection. However some of the preliminary symptoms that could indicate signs of ovarian cancer are- abdominal pain, bloating, and feeling full very suddenly and abruptly (Goff et al., 2004).
A standard treatment option for ovarian cancer is surgery followed by chemotherapy. The goal to operate on the tumor first is to reduce the bulk of the tumor mass and then kill all the remaining cells with drugs through chemotherapy. The problem that this treatment plans faces is that different patients react to chemotherapy drugs differently with many showing tumor drug resistances.

Advancements in genomic studies have helped us identify epigenetic markers that could be narrowed down as therapeutic targets for molecular subtypes of ovarian cancer- these biomarker targeted therapies could show a

different response than the ones normally recorded (Bell et al., 2011). For instance, high-grade serous carcinoma has a characteristic TP53 mutation with frequent copy number alterations, while mutations in ARID1A and PIK3CA are characteristic in clear cell ovarian carcinoma (S. Zhang et al., 2019).

The lethality of ovarian cancer makes it a very sought after area of research for targeted therapy. Among the numerous targeted therapies approved for the treatment of ovarian cancer, one of them is treating patients with high-grade serous carcinoma with anti-angiogenic agents and PARP inhibitors for patients with BRCA mutations (Lopez et al., 2013).

Conclusively, ovarian cancer is highly lethal. Existing treatments for advanced stage ovarian have shown drawbacks in the form of treatment resistance, tumor recurrence and cancer metastasis. Epigenetic biomarkers have opened new avenues to develop novel therapeutic options which can prove to be highly efficient.

PCOS: Polycystic Ovarian Syndrome

PCOS is a common endocrine disorder that affects around 10% of women in their reproductive age (Teede et al., 2010). This condition has multiple characteristics such as the presence of multiple ovarian cysts, irregularity in menstrual cycles and an increased expression of androgen hormones. PCOS has a very significant influence on the fertility and the overall reproductive health of a woman.

We haven't yet been able to pinpoint the exact cause of PCOS, but studies have established underlying factors of insulin resistance and a high level of androgen hormone production (Dumesic et al., 2015). Women with PCOS have a higher risk of contracting other diseases such as type 2 diabetes, heart problems and an increased blood pressure (Legro et al., 2013).

A combination of clinical and laboratory criteria is involved in the diagnosis of PCOS. The Rotterdam criteria are generally used to diagnose PCOS which involves exhibiting at least two of the following symptoms- the presence of polycystic ovaries through an ultrasound scan, clinical evidence of hyperandrogenism, or having irregular menstrual periods (Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group, 2004).

PCOS can be approached through many multidisciplinary techniques for lifestyle modifications such as- exercise, weight loss, pharmacological interventions like oral contraceptives and insulin-sensitizing supplements (Lanzo et al., 2015). Additionally, women with PCOS attempting to conceive children might have to opt for assisted reproductive technology like IVF.

PCOS is a complex disorder that expresses itself in different ways in different women. It can have a significant impact on the quality of an affected woman's life. People with PCOS have a really pressing need to receive appropriate care and assistance in monitoring and managing any associated health disorder.

HIF-1α

Hypoxia-inducible-factor-1α is a transcription factor plays a very crucial role in cancer development and progression. It is activated in cellular response to hypoxia- a state in which oxygen is not available in sufficient amounts to maintain homeostasis (Bhutta et al., 2023). This subsequently leads to an upregulation of genes that promote cell survival, metastasis and angiogenesis. HIF-1α has a high expression in numerous types of cancer such as ovarian, breast, lung and prostrate. This over-expression in cancers has been associated to poor prognosis and very high lethality for patients (Semenza, 2012)·(Keith et al., 2011).

HIF-1α assists in tumour growth, progression and metastasis by upregulating numerous cellular pathways such as angiogenesis, apoptosis and glycolysis.

- It promotes and enhances glycolysis by the upregulation of the expression of glycolytic enzymes and glucose transporters which provides energy for the metabolism of cancer cells in hypoxic conditions.
- HIF-1α also upregulates the expression of vascular endothelial growth factor (VEGF) which subsequently promotes angiogenesis.
- HIF-1α aids in the inhibition of programmed cell death or apoptosis by promoting the expression of anti-apoptotic proteins and inhibiting the functioning of pro-apoptotic proteins (Brahimi-Horn et al., 2007).

HIF-1α in Ovarian Cancer

Studies have shown that there is a higher expression of HIF-1α in ovarian cancer cells than normal ovarian cells. This over expression is associated with high lethality and poor prognosis, and resistance to treatment like chemotherapy (Muz et al., 2015)·(H. Zhang et al., 2019). Additionally, this transcription factor exhibited higher expression in advanced stage cancer than early-stage cancer (X. Wang et al., 2021).

Several studies have reported a positive correlation between HIF-1α and the expression of VEGF in ovarian cancer (Ranjbar et al., 2015),(Birner et al., 2001). HIF-1α upregulates the expression of VEGF which subsequently contributes to angiogenesis which is a hallmark of cancer cells (Lv et al., 2016). HIF-1α also promotes the expression of platelet-derived growth factors (PDGF) which in turn promotes the proliferation and migration of endothelial cells (Brahimi-Horn et al., 2007).

In addition to promoting VEGF and hence angiogenesis, HIF-1α also regulates cell proliferation and their survival in ovarian cancer cells by upregulating the expression of anti-apoptotic genes (Greijer & van der Wall, 2004) and the genes involved in cell cycle progression (Koshiji et al., 2004). HIF-1α upregulates anti-apoptotic proteins such as Bcl-2 and Mcl-1 and downregulates the pro-apoptotic proteins including Bad and Bax (Sermeus et al., 2012).
The cellular process involving the degradation and recycling of cellular components to maintain homeostasis in cells is called autophagy. HIF-1α has been associated with cellular autophagy by the upregulation of numerous autophagy-related genes such as Beclin-1 and LCB3 which leads to an increase in autophagic activity (Alvarez-Meythaler et al., 2020) in ovarian cancer cells.

HIF-1α also plays a critical role in the regulation of glycolysis where it upregulates the expression of glucose transporters like GLUT1 and GLUT3 which leads to increased glucose metabolism and uptake (Semenza, 2012). This increase subsequently aids in satisfying the high energy demands of cancer cells. Conclusively, HIF-1α is a promising therapeutic target for the treatment of ovarian cancer.

HIF-1α in Polycystic Ovarian Syndrome (PCOS)

Apart from the very critical role that HIF-1α transcription factor plays in cancer progression and proliferation, there has recently been a growing interest in the correlation of HIF-1α in association with the pathogenesis of PCOS. HIF-1α has been known to regulate several cellular pathways that assist in the development and progression of PCOS which includes insulin resistance, inflammation and hyperandrogenism.

One of the hallmark characteristics of PCOS is insulin resistance which influences the development and progression of metabolic disorders such as type 2 diabetes and several cardiovascular diseases. Many recent studies have shown that HIF-1α significantly regulates insulin sensitivity by the upregulation of the expression of numerous genes associated with glucose metabolism like the glucose transporter GLUT1 and insulin receptor substrate IRS-1(Shaw, 2011)·(He et al., 2011). In many animal models, targeting HIF-1α has shown a significant improvement in insulin sensitivity and in reducing hyperandrogenism (McDonald et al., 2022).

Another key component to the pathophysiology of PCOS is inflammation. HIF-1α regulates the expression of numerous pro-inflammatory cytokines such a tumour necrosis factor-alpha (TNF-α), interleukin-1ß (IL-1ß) and

interleukin-6 (IL-6) (Zafari Zangeneh et al., 2017). Another pro-inflammatory cellular process- NF-kß signalling pathway plays a very vital role in inflammatory regulation. This pathway is activated by HIF-1α according to multiple studies (*HIF Transcription Factors, Inflammation, and Immunity - PMC*, n.d.).

Hyperandrogenism is a defining characteristic of PCOS. It is defined as an increased rate of androgen production in a woman. HIF-1α influences the regulation of androgen biosynthesis by aiding in the upregulation of the expression of numerous enzymes like 3-beta-hydroxysteroid dehydrogenase type 2 (HSD3B2) and cytochrome P450 family 17 subfamily A member 1 (CYP17A1) (Zhou et al., 2021).

KDM3A

KDM3A is an epigenetic factor also known as JHDM2A or JMJD1A. It is a lysine demethylase enzyme belonging to the protein family containing the Jumonji domain. It plays a very critical role in gene expression regulation by demethylating histone H3K9me1/2 and H3K36me2 which leads to transcriptional activation.

KDM3A was initially recognised as a transcription co-activator due to its interaction with the androgen receptor (AR) which subsequently promoted AR-mediated gene expression in cells of prostate cancer (Yamane et al., 2006). Studies conducted since then have shown that KDM3A is associated with the regulation of a number of biological processes like cell proliferation and differentiation, and programmed cell death or apoptosis. For example, KDM3A has exhibited properties of promotion in the differentiation of myoblasts by influencing the expression of myogenic genes(Krieg et al., 2010). It also inhibits the proliferation of tumour cells in breast cancer by the suppression of cyclin D1 expression (Yoo et al., 2020). KDM3A is also associated with processes like adipogenesis (Okamura et al., 2010), neuronal differentiation (Wilson et al., 2017) and spermatogenesis (Kim et al., 2018a).

This epigenetic transcription factor is involved in gene activation by demethylating transcription-inhibiting repressive histone markers H3K9me1/2 and H3K36me2 (Klose et al., 2006). KDM3A influences the promoter region of target genes by recruiting transcriptional co-activators like p300/CBP and MED1 by binding to specific DNA sequences like androgen response elements (AREs) (Okada et al., 2007). This process subsequently leads to histone acetylation allows open access to RNA polymerase II and other transcriptional machinery to the gene promoter which ultimately results in gene expression activation (Wade et al., 2015).

The dysfunction and dysregulation of KDM3A has been associated with various diseases like neurological disorders, cancer and other metabolic diseases. Take for instance, a stark overexpression of KDM3A has been witnessed in several types of cancer like breast cancer (Humphries et al., 2019), prostate cancer (Zhan et al., 2016) and leukaemia (Kim et al., 2018b), and has also been associated with cell proliferation and migration which enhances tumour growth and metastasis.

Recent studies have also indicated that KDM3A influences the expression of genes regulating synaptic function and neuroinflammation making it a critical therapeutic target for many neurodegenerative disorders such as Alzheimer's and Parkinson's (Basavarajappa & Subbanna, 2021).

Lastly, a deficiency in KDM3A has been associated with resistance to insulin and obesity, and dysfunctional spermatogenesis and male infertility (Hojati et al., 2019).

Conclusively, KDM3A is a versatile epigenetic factor that is associated with the cellular and molecular prognosis of multiple disorders making it a highly potential candidate for therapeutic targets.

KDM3A in Ovarian Cancer

KDM3A plays a critical role in transcriptional regulation, cell differentiation and stemness making it a significant epigenetic factor associated with ovarian cancer.

Studies in ovarian cancer have led to a correlation between the overexpression of KDM3A with cell proliferation, tumour migration and invasion and resistance to treatment along with tumour recurrence (Yang et al., 2018). An

upregulation of KDM3A in ovarian cancer tissues as compared to normal tissues is also linked with a poorer prognosis in ovarian cancer patients (Yoo et al., 2020).

In certain studies, silencing of KDM3A in ovarian cancer cells prevents cell proliferation and tumour migration which provides a cementing role for KDM3A in the progression of ovarian cancer (Ramadoss et al., 2017). Another study suggested that KDM3A plays a role in the promotion of growth and invasion of ovarian cancer cells by influencing the expression of PTEN, a tumour supressing gene. PTEN is an essential regulator of the PI3K/AKT pathway and is often mutated or deleted in ovarian cancer which promotes cell growth and survival. The study indicated that KDM3A directly binds to the PTEN promoter region which decreases PTEN expression which leads to the activation of the PI3K/AKT pathway (Nero et al., 2019).

KDM3A also plays a vital role in DNA damage response in ovarian cancer cells. One study showed that the depletion of KDM3A vastly increased the sensitivity of ovarian cancer cells making them more prone to DNA damage-induced apoptosis. This directly correlates the involvement of KDM3A with the development of chemoresistance which poses as a major obstacle in ovarian cancer treatment (Mirza-Aghazadeh-Attari et al., 2019).

One other study demonstrated that KDM3A increases the rate of metastasis in ovarian cancer by influencing the epithelial to mesenchymal transition (EMT) process. KDM3A upregulates Snail and Slug, transcription factors that activate EMT and promote invasion of cancer cells into other tissues. The study also highlighted that silencing KDM3A inhibits the EMT process and in turn decreases the invasive characteristics of ovarian cancer cells (Ottevanger, 2017). All the more, a recent study highlighted that the KDM3A epigenetic factor influences the expression of CD133, a cancer stem cell marker exhibited in ovarian cancer. This study revealed that the silencing of KDM3A influences the expression of CD133 by inhibiting it that subsequently supresses the self-renewal capabilities of ovarian cancer cells along with the initiation of the tumour (Kaniskan et al., 2018). This study also stated that KDM3A plays a very important role to immunize the ovarian cancer cells to the effects of chemotherapy drugs by influencing the impact of multi-drug resistance (MDR) proteins (N. Wang et al., 2023). This proves that KDM3A is a key player in ovarian cancer stemness and resistance to treatment.

In conclusion, KDM3A is a very important epigenetic factor that can vastly influence the progression of ovarian cancer and understanding its molecular mechanism may lead to development of effective therapies to combat ovarian cancer.

KDM3A in PCOS

One of the hallmarks of polycystic ovarian syndrome is hormonal dysregulation which is characterized by hormonal dysregulation, including elevated androgens, disrupted gonadotropin secretion, and impaired oestrogen metabolism. KDM3A interacts with important regulators of hormone production and signalling pathways, such as aromatase, steroidogenic factor-1 (SF-1), and follicle-stimulating hormone (FSH). Research indicates that KDM3A may play a role in the abnormal hormonal profile seen in PCOS by influencing the expression of genes involved in steroidogenesis and hormone receptor signalling (Throwba et al., 2022).

Another prominent feature of PCOS is aberrant follicular development with multiple cyst formation. KDM3A is involved in the regulation of genes responsible for granulosa cell proliferation, steroid biosynthesis, and oocyte maturation, thereby impacting follicular growth and development. Studies utilizing KDM3A knockout models have demonstrated disturbances in folliculogenesis and changes in the expression of crucial genes associated with follicle development, providing additional evidence of its involvement in the development of PCOS (Roy et al., 2021).

Insulin resistance is a prevalent metabolic disturbance seen in PCOS, which contributes to an increased susceptibility to type 2 diabetes and cardiovascular complications. KDM3A has been implicated in modulating insulin signalling pathways and maintaining the balance of glucose in the body. Studies have demonstrated that the absence of KDM3A in the liver and adipose tissue improves insulin sensitivity and reduces adiposity. These findings suggest a potential link between KDM3A and insulin resistance in the context of PCOS (*(PDF) MiRNAs Regulating Insulin*

Sensitivity Are Dysregulated in Polycystic Ovary Syndrome (PCOS) Ovaries and Are Associated With Markers of Inflammation and Insulin Sensitivity, n.d.).

Numerous studies have investigated the therapeutic possibilities of targeting KDM3A in PCOS. Researchers have developed small molecule inhibitors of KDM3A that effectively suppress androgen production and reinstate healthy ovarian function in preclinical models of PCOS. Moreover, gene editing techniques like CRISPR-Cas9 have been utilized to specifically hinder KDM3A expression in animal models of PCOS, resulting in enhanced reproductive and metabolic outcomes. Nevertheless, additional research is required to assess the safety and efficacy of KDM3A-targeted therapies in human subjects (Gutierrez et al., 2022).

Biological interplay between HIF-1α and KDM3A in the development and progression of ovarian cancer

The association between HIF-1α and KDM3A in ovarian cancer arises from their reciprocal regulation. HIF-1α has the ability to directly modulate KDM3A expression by binding to specific regions within the promoter of the KDM3A gene. This binding event triggers the activation of KDM3A transcription, leading to an increase in KDM3A protein levels in ovarian cancer cells. Elevated KDM3A expression, in turn, fosters various tumour-promoting processes, including enhanced cell proliferation, angiogenesis, and metastasis (Ikeda et al., 2018).

Notably, KDM3A also exerts an influence on HIF-1α stability and activity. Studies have demonstrated that KDM3A physically interacts with HIF-1α and serves as a demethylase for particular lysine residues on HIF-1α. By demethylating HIF-1α, KDM3A impedes its hydroxylation and subsequent degradation, resulting in its stabilization and augmented transcriptional activity. Consequently, the activation of genes targeted by HIF-1α is further amplified, thereby promoting tumour progression and facilitating adaptation to the hypoxic microenvironment within tumours (Salminen et al., 2016).

This intricate interplay between HIF-1α and KDM3A generates a positive feedback loop, reinforcing their reciprocal activation and driving the aggressive behaviour of ovarian cancer cells. The increased expression of KDM3A triggered by HIF-1α contributes to the sustained stability and activity of HIF-1α, intensifying its transcriptional effects on genes implicated in angiogenesis, metabolism, and invasiveness.

Furthermore, the interaction between HIF-1α and KDM3A in ovarian cancer extends beyond direct regulation, encompassing complex signalling networks and cross-talk with other crucial pathways. For example, the PI3K/Akt pathway, which frequently undergoes dysregulation in cancer, can modulate the stability and activity of both HIF-1α and KDM3A. Activation of the PI3K/Akt signalling pathway can enhance the expression and function of HIF-1α and KDM3A, further fuelling tumour growth and progression (Jun et al., 2017).

Biological interplay between HIF-1α and KDM3A in the development and progression of polycystic ovarian syndrome (PCOS)

The interaction between HIF-1α and KDM3A in PCOS involves multiple mechanisms that influence the development and progression of the syndrome. Firstly, HIF-1α directly controls the expression of KDM3A by binding to specific regions within the KDM3A promoter. This binding event results in increased levels of KDM3A, which, in turn, affects the expression of genes involved in hormone production and signalling.

Additionally, KDM3A can impact the activity of HIF-1α through epigenetic modifications. Research has demonstrated that KDM3A can regulate the methylation status of specific lysine residues on HIF-1α, leading to changes in its stability and transcriptional activity. By demethylating HIF-1α, KDM3A promotes its stabilization and enhances its ability to activate target genes that play a role in processes such as angiogenesis, metabolism, and other relevant aspects of PCOS.

The interplay between HIF-1α and KDM3A has significant implications for the progression of PCOS. Dysregulated signalling of HIF-1α and KDM3A can contribute to the development of ovarian cysts, impaired follicular growth, and excessive production of androgens, which are characteristic features of PCOS. Moreover, the dysregulation of these factors can also lead to insulin resistance, a metabolic disturbance commonly observed in individuals with PCOS.

Understanding the intricate interplay between HIF-1α and KDM3A in PCOS sheds light on the underlying molecular mechanisms involved in the syndrome. It highlights the role of HIF-1α-mediated gene regulation and KDM3A-mediated epigenetic modifications in the development and progression of PCOS. Disruptions in these interrelated pathways can contribute to the hormonal imbalances, impaired follicular development, and metabolic disturbances observed in PCOS.

Further research is needed to unravel the precise molecular mechanisms and signalling pathways underlying the interplay between HIF-1α and KDM3A in PCOS. Elucidating these mechanisms can provide valuable insights into the pathogenesis of PCOS and potentially lead to the development of novel therapeutic strategies that target HIF-1α and KDM3A signalling pathways. Ultimately, these interventions may help restore hormonal balance, improve ovarian function, and alleviate the metabolic disturbances associated with PCOS.

Limitations and challenges of targeting HIF-1α and KDM3A in ovarian cancer therapy

Targeting HIF-1α and KDM3A in cancer therapy poses challenges due to their involvement in multiple cellular processes, including those essential for normal physiological functions. Inhibiting these molecules could potentially disrupt crucial cellular processes, leading to unintended and undesirable side effects.

Firstly, maintaining the selectivity and specificity of therapeutic agents that target HIF-1α and KDM3A is of utmost importance to minimize off-target effects and potential toxicity. The task of developing inhibitors that specifically target cancer cells while sparing normal cells expressing these molecules is a significant challenge.

Secondly, ovarian cancer is characterized by significant heterogeneity, with different subtypes and genetic alterations. The expression and regulation of HIF-1α and KDM3A may vary among different ovarian cancer subtypes, making it essential to identify patient populations most likely to benefit from HIF-1α and KDM3A-targeted therapies. Additionally, at present, there is a shortage of dependable biomarkers that can accurately predict the response of patients to HIF-1α and KDM3A-targeted therapies. The identification and validation of reliable predictive biomarkers are essential for effectively stratifying patients and selecting appropriate treatments.

The development of resistance mechanisms is also a common occurrence in cancer cells when exposed to targeted therapies. Similarly, HIF-1α and KDM3A-targeted therapies may face similar challenges, as cancer cells have the potential to develop resistance to these interventions over time, thereby diminishing their long-term effectiveness. Another challenge faced while using epigenetic factors as a mode of therapy is the delivery mechanism- the effective and targeted delivery of therapeutic agents to tumour cells continues to be a significant limitation. It is essential to develop strategies that improve drug delivery specifically to the tumour site while minimizing the potential for systemic toxicity. Such approaches are crucial for the successful translation of these therapies into clinical practice.

Similarly, due to the intricate characteristics of ovarian cancer, the use of combination therapies may offer greater efficacy compared to single-agent approaches. Identifying appropriate combination partners, optimizing dosing regimens, and addressing potential drug interactions are essential factors to consider for the successful implementation of combination therapies involving HIF-1α and KDM3A-targeted agents.

Lastly, the transition from preclinical studies to clinical trials and the eventual integration of HIF-1α and KDM3A-targeted therapies into standard clinical practice necessitate thorough assessment through well-designed clinical trials. This rigorous evaluation should encompass the investigation of safety profiles, efficacy, and long-term outcomes to ensure the reliable and effective use of these therapies in a clinical setting.

Limitations and challenges of targeting HIF-1α and KDM3A in PCOS therapy

A major obstacle in targeting HIF-1α and KDM3A in PCOS is the need to achieve selectivity while minimizing off-target effects. Both HIF-1α and KDM3A play roles in various physiological processes beyond PCOS, and interfering with their functions can disrupt normal cellular processes and lead to undesired side effects. Therefore, it is crucial to develop therapeutic agents that specifically target HIF-1α and KDM3A in the context of PCOS, while sparing their physiological roles in other tissues and organs. Ensuring the selectivity and specificity of these agents is vital to mitigate off-target effects and minimize potential toxicity.

Another limitation stems from the complex and multifactorial nature of PCOS. PCOS is a heterogeneous disorder with diverse underlying mechanisms and clinical manifestations, making it challenging to identify the most suitable therapeutic targets. HIF-1α and KDM3A are just two of many molecules implicated in the pathogenesis of PCOS, and their roles may vary among individuals. Therefore, a personalized approach that considers individual patient characteristics and molecular profiles may be necessary to effectively target HIF-1α and KDM3A in PCOS.

Resistance to targeted therapies is a common challenge observed in various diseases, including cancer, and it may also arise in the context of PCOS therapy targeting HIF-1α and KDM3A. Cancer cells, as well as the dysregulated molecular pathways in PCOS, can develop mechanisms to bypass or overcome the effects of targeted therapies, resulting in treatment resistance and disease progression. Over time, the dysregulated pathways involving HIF-1α and KDM3A in PCOS may undergo adaptive changes, reducing the effectiveness of targeted interventions. Therefore, it is crucial to gain a comprehensive understanding of the underlying mechanisms of resistance and develop strategies to overcome or prevent it. By doing so, we can enhance the long-term success of HIF-1α and KDM3A-targeted therapies in PCOS.

Conclusion

Ovarian cancer and PCOS pose significant challenges to women's health, necessitating the development of novel therapeutic approaches. Targeting HIF-1α and KDM3A has shown promise due to their pivotal roles in disease progression. Both HIF-1α and KDM3A contribute to essential processes such as angiogenesis, cell proliferation, and metabolic dysregulation, which underlie the pathogenesis of ovarian cancer and PCOS. Accumulating evidence from preclinical and clinical studies demonstrates the therapeutic potential of inhibiting HIF-1α and KDM3A in these conditions. However, further research is needed to fully elucidate the precise mechanisms and optimize the efficacy of these inhibitors. By unravelling the intricate interplay between HIF-1α, KDM3A, and disease progression, researchers can pave the way for targeted therapies that enhance outcomes for ovarian cancer and PCOS patients. Ultimately, exploring these innovative therapeutic avenues holds great promise for transforming the management of these challenging conditions and improving the quality of life for affected individuals.

References

1. Alvarez-Meythaler, J. G., Garcia-Mayea, Y., Mir, C., Kondoh, H., & LLeonart, M. E. (2020). Autophagy Takes Center Stage as a Possible Cancer Hallmark. *Frontiers in Oncology*, *10*. https://www.frontiersin.org/articles/10.3389/fonc.2020.586069
2. Basavarajappa, B. S., & Subbanna, S. (2021). Histone Methylation Regulation in Neurodegenerative Disorders. *International Journal of Molecular Sciences*, *22*(9), 4654. https://doi.org/10.3390/ijms22094654
3. Bell, D., Berchuck, A., Birrer, M., Chien, J., Cramer, D. W., Dao, F., Dhir, R., DiSaia, P., Gabra, H., Glenn, P., Godwin, A. K., Gross, J., Hartmann, L., Huang, M., Huntsman, D. G., Iacocca, M., Imielinski, M., Kalloger, S., Karlan, B. Y., … Data coordination centre. (2011). Integrated genomic analyses of ovarian carcinoma. *Nature*, *474*(7353), Article 7353. https://doi.org/10.1038/nature10166

4. Bhutta, B. S., Alghoula, F., & Berim, I. (2023). Hypoxia. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK482316/
5. Birner, P., Schindl, M., Obermair, A., Breitenecker, G., & Oberhuber, G. (2001). Expression of hypoxia-inducible factor 1alpha in epithelial ovarian tumors: Its impact on prognosis and on response to chemotherapy. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, *7*(6), 1661–1668.
6. Bowtell, D. D., Böhm, S., Ahmed, A. A., Aspuria, P.-J., Bast, R. C., Beral, V., Berek, J. S., Birrer, M. J., Blagden, S., Bookman, M. A., Brenton, J. D., Chiappinelli, K. B., Martins, F. C., Coukos, G., Drapkin, R., Edmondson, R., Fotopoulou, C., Gabra, H., Galon, J., … Balkwill, F. R. (2015). Rethinking ovarian cancer II: Reducing mortality from high-grade serous ovarian cancer. *Nature Reviews Cancer*, *15*(11), Article 11. https://doi.org/10.1038/nrc4019
7. Brahimi-Horn, M. C., Chiche, J., & Pouysségur, J. (2007). Hypoxia and cancer. *Journal of Molecular Medicine (Berlin, Germany)*, *85*(12), 1301–1307. https://doi.org/10.1007/s00109-007-0281-3
8. Dumesic, D. A., Oberfield, S. E., Stener-Victorin, E., Marshall, J. C., Laven, J. S., & Legro, R. S. (2015). Scientific Statement on the Diagnostic Criteria, Epidemiology, Pathophysiology, and Molecular Genetics of Polycystic Ovary Syndrome. *Endocrine Reviews*, *36*(5), 487–525. https://doi.org/10.1210/er.2015-1018
9. Goff, B. A., Mandel, L. S., Melancon, C. H., & Muntz, H. G. (2004). Frequency of symptoms of ovarian cancer in women presenting to primary care clinics. *JAMA*, *291*(22), 2705–2712. https://doi.org/10.1001/jama.291.22.2705
10. Greijer, A. E., & van der Wall, E. (2004). The role of hypoxia inducible factor 1 (HIF-1) in hypoxia induced apoptosis. *Journal of Clinical Pathology*, *57*(10), 1009–1014. https://doi.org/10.1136/jcp.2003.015032
11. Gutierrez, K., Glanzner, W., Priotto de Macedo, M., Braga, V., Dicks, N., Bohrer, R., Baldassarre, H., Agellon, L., & Bordignon, V. (2022). Cell Cycle Stage and DNA Repair Pathway Influence CRISPR/Cas9 Gene Editing Efficiency in Porcine Embryos. *Life*, *12*, 171. https://doi.org/10.3390/life12020171
12. He, Q., Gao, Z., Yin, J., Zhang, J., Yun, Z., & Ye, J. (2011). Regulation of HIF-1α activity in adipose tissue by obesity-associated factors: Adipogenesis, insulin, and hypoxia. *American Journal of Physiology - Endocrinology and Metabolism*, *300*(5), E877–E885. https://doi.org/10.1152/ajpendo.00626.2010
13. *HIF Transcription Factors, Inflammation, and Immunity—PMC*. (n.d.). Retrieved April 9, 2023, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4346319/
14. Hojati, Z., Soleimanpour, E., Javadirad, S.-M., & Nasr-Esfahani, M. H. (2019). Identification of Two Novel Mutations in KDM3A Regulatory Gene in Iranian Infertile Males. *Iranian Biomedical Journal*, *23*(3), 220–227. https://doi.org/10.29252/.23.3.220
15. Humphries, B., Wang, Z., & Yang, C. (2019). MicroRNA Regulation of Epigenetic Modifiers in Breast Cancer. *Cancers*, *11*(7), 897. https://doi.org/10.3390/cancers11070897
16. Ikeda, S., Kitadate, A., Abe, F., Takahashi, N., & Tagawa, H. (2018). Hypoxia-inducible KDM3A addiction in multiple myeloma. *Blood Advances*, *2*(4), 323–334. https://doi.org/10.1182/bloodadvances.2017008847
17. Jun, J. C., Rathore, A., Younas, H., Gilkes, D., & Polotsky, V. Y. (2017). Hypoxia-Inducible Factors and Cancer. *Current Sleep Medicine Reports*, *3*(1), 1–10. https://doi.org/10.1007/s40675-017-0062-7
18. Kaniskan, H. Ü., Martini, M. L., & Jin, J. (2018). Inhibitors of Protein Methyltransferases and Demethylases. *Chemical Reviews*, *118*(3), 989–1068. https://doi.org/10.1021/acs.chemrev.6b00801
19. Keith, B., Johnson, R. S., & Simon, M. C. (2011). HIF1α and HIF2α: Sibling rivalry in hypoxic tumour growth and progression. *Nature Reviews. Cancer*, *12*(1), 9–22. https://doi.org/10.1038/nrc3183
20. Kim, H., Kim, D., Choi, S. A., Kim, C. R., Oh, S. K., Pyo, K. E., Kim, J., Lee, S.-H., Yoon, J.-B., Zhang, Y., & Baek, S. H. (2018a). KDM3A histone demethylase functions as an essential factor for activation of JAK2−STAT3 signaling pathway. *Proceedings of the National Academy of Sciences*, *115*(46), 11766–11771. https://doi.org/10.1073/pnas.1805662115

21. Kim, H., Kim, D., Choi, S. A., Kim, C. R., Oh, S. K., Pyo, K. E., Kim, J., Lee, S.-H., Yoon, J.-B., Zhang, Y., & Baek, S. H. (2018b). KDM3A histone demethylase functions as an essential factor for activation of JAK2−STAT3 signaling pathway. *Proceedings of the National Academy of Sciences of the United States of America*, *115*(46), 11766–11771. https://doi.org/10.1073/pnas.1805662115
22. Klose, R. J., Kallin, E. M., & Zhang, Y. (2006). JmjC-domain-containing proteins and histone demethylation. *Nature Reviews Genetics*, *7*(9), Article 9. https://doi.org/10.1038/nrg1945
23. Koshiji, M., Kageyama, Y., Pete, E. A., Horikawa, I., Barrett, J. C., & Huang, L. E. (2004). HIF-1α induces cell cycle arrest by functionally counteracting Myc. *The EMBO Journal*, *23*(9), 1949–1956. https://doi.org/10.1038/sj.emboj.7600196
24. Krieg, A. J., Rankin, E. B., Chan, D., Razorenova, O., Fernandez, S., & Giaccia, A. J. (2010). Regulation of the Histone Demethylase JMJD1A by Hypoxia-Inducible Factor 1α Enhances Hypoxic Gene Expression and Tumor Growth. *Molecular and Cellular Biology*, *30*(1), 344–353. https://doi.org/10.1128/MCB.00444-09
25. Kurman, R. J., & Shih, I.-M. (2016). The Dualistic Model of Ovarian Carcinogenesis: Revisited, Revised, and Expanded. *The American Journal of Pathology*, *186*(4), 733–747. https://doi.org/10.1016/j.ajpath.2015.11.011
26. Lanzo, E., Monge, M., & Trent, M. (2015). Diagnosis and Management of Polycystic Ovary Syndrome in Adolescent Girls. *Pediatric Annals*, *44*(9), e223–e230. https://doi.org/10.3928/00904481-20150910-10
27. Legro, R. S., Arslanian, S. A., Ehrmann, D. A., Hoeger, K. M., Murad, M. H., Pasquali, R., Welt, C. K., & Endocrine Society. (2013). Diagnosis and treatment of polycystic ovary syndrome: An Endocrine Society clinical practice guideline. *The Journal of Clinical Endocrinology and Metabolism*, *98*(12), 4565–4592. https://doi.org/10.1210/jc.2013-2350
28. Lopez, J., Banerjee, S., & Kaye, S. B. (2013). New developments in the treatment of ovarian cancer—Future perspectives. *Annals of Oncology*, *24*(Suppl 10), x69–x76. https://doi.org/10.1093/annonc/mdt475
29. Lv, X., Li, J., Zhang, C., Hu, T., Li, S., He, S., Yan, H., Tan, Y., Lei, M., Wen, M., & Zuo, J. (2016). The role of hypoxia-inducible factors in tumor angiogenesis and cell metabolism. *Genes & Diseases*, *4*(1), 19–24. https://doi.org/10.1016/j.gendis.2016.11.003
30. McDonald, P. C., Chafe, S. C., Supuran, C. T., & Dedhar, S. (2022). Cancer Therapeutic Targeting of Hypoxia Induced Carbonic Anhydrase IX: From Bench to Bedside. *Cancers*, *14*(14), Article 14. https://doi.org/10.3390/cancers14143297
31. Menon, U., Karpinskyj, C., & Gentry-Maharaj, A. (2018). Ovarian Cancer Prevention and Screening. *Obstetrics and Gynecology*, *131*(5), 909–927. https://doi.org/10.1097/AOG.0000000000002580
32. Mirza-Aghazadeh-Attari, M., Ostadian, C., Saei, A. A., Mihanfar, A., Darband, S. G., Sadighparvar, S., Kaviani, M., Samadi Kafil, H., Yousefi, B., & Majidinia, M. (2019). DNA damage response and repair in ovarian cancer: Potential targets for therapeutic strategies. *DNA Repair*, *80*, 59–84. https://doi.org/10.1016/j.dnarep.2019.06.005
33. Muz, B., de la Puente, P., Azab, F., & Azab, A. K. (2015). The role of hypoxia in cancer progression, angiogenesis, metastasis, and resistance to therapy. *Hypoxia*, *3*, 83–92. https://doi.org/10.2147/HP.S93413
34. Nero, C., Ciccarone, F., Pietragalla, A., & Scambia, G. (2019). PTEN and Gynecological Cancers. *Cancers*, *11*(10), Article 10. https://doi.org/10.3390/cancers11101458
35. Okada, Y., Scott, G., Ray, M. K., Mishina, Y., & Zhang, Y. (2007). Histone demethylase JHDM2A is critical for Tnp1 and Prm1 transcription and spermatogenesis. *Nature*, *450*(7166), 119–123. https://doi.org/10.1038/nature06236
36. Okamura, M., Inagaki, T., Tanaka, T., & Sakai, J. (2010). Role of histone methylation and demethylation in adipogenesis and obesity. *Organogenesis*, *6*(1), 24–32.
37. Ottevanger, P. B. (2017). Ovarian cancer stem cells more questions than answers. *Seminars in Cancer Biology*, *44*, 67–71. https://doi.org/10.1016/j.semcancer.2017.04.009

38. *(PDF) MiRNAs Regulating Insulin Sensitivity Are Dysregulated in Polycystic Ovary Syndrome (PCOS) Ovaries and Are Associated With Markers of Inflammation and Insulin Sensitivity*. (n.d.). Retrieved May 31, 2023, from https://www.researchgate.net/publication/337921398_MiRNAs_Regulating_Insulin_Sensitivity_Are_Dysregulated_in_Polycystic_Ovary_Syndrome_PCOS_Ovaries_and_Are_Associated_With_Markers_of_Inflammation_and_Insulin_Sensitivity
39. Ramadoss, S., Sen, S., Ramachandran, I., Roy, S., Chaudhuri, G., & Farias-Eisner, R. (2017). Lysine-specific demethylase KDM3A regulates ovarian cancer stemness and chemoresistance. *Oncogene*, *36*(11), 1537–1545. https://doi.org/10.1038/onc.2016.320
40. Ranjbar, R., Nejatollahi, F., Nedaei Ahmadi, A. S., Hafezi, H., & Safaie, A. (2015). Expression of Vascular Endothelial Growth Factor (VEGF) and Epidermal Growth Factor Receptor (EGFR) in Patients With Serous Ovarian Carcinoma and Their Clinical Significance. *Iranian Journal of Cancer Prevention*, *8*(4), e3428. https://doi.org/10.17795/ijcp-3428
41. Rotterdam ESHRE/ASRM-Sponsored PCOS consensus workshop group. (2004). Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). *Human Reproduction (Oxford, England)*, *19*(1), 41–47. https://doi.org/10.1093/humrep/deh098
42. Roy, S., Huang, B., Sinha, N., Wang, J., & Sen, A. (2021). Androgens regulate ovarian gene expression by balancing Ezh2-Jmjd3 mediated H3K27me3 dynamics. *PLoS Genetics*, *17*(3), e1009483. https://doi.org/10.1371/journal.pgen.1009483
43. Salminen, A., Kaarniranta, K., & Kauppinen, A. (2016). Hypoxia-Inducible Histone Lysine Demethylases: Impact on the Aging Process and Age-Related Diseases. *Aging and Disease*, *7*(2), 180–200. https://doi.org/10.14336/AD.2015.0929
44. Semenza, G. L. (2012). Hypoxia-inducible factors: Mediators of cancer progression and targets for cancer therapy. *Trends in Pharmacological Sciences*, *33*(4), 207–214. https://doi.org/10.1016/j.tips.2012.01.005
45. Sermeus, A., Genin, M., Maincent, A., Fransolet, M., Notte, A., Leclere, L., Riquier, H., Arnould, T., & Michiels, C. (2012). Hypoxia-Induced Modulation of Apoptosis and BCL-2 Family Proteins in Different Cancer Cell Types. *PLOS ONE*, *7*(11), e47519. https://doi.org/10.1371/journal.pone.0047519
46. Shaw, L. M. (2011). The insulin receptor substrate (IRS) proteins. *Cell Cycle*, *10*(11), 1750–1756. https://doi.org/10.4161/cc.10.11.15824
47. Siegel, R. L., Miller, K. D., & Jemal, A. (2020). Cancer statistics, 2020. *CA: A Cancer Journal for Clinicians*, *70*(1), 7–30. https://doi.org/10.3322/caac.21590
48. Teede, H., Deeks, A., & Moran, L. (2010). Polycystic ovary syndrome: A complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. *BMC Medicine*, *8*(1), 41. https://doi.org/10.1186/1741-7015-8-41
49. Throwba, H., Unnikrishnan, L., Pangath, M., Vasudevan, K., Jayaraman, S., Li, M., Iyaswamy, A., Palaniyandi, K., & Gnanasampanthapandian, D. (2022). The epigenetic correlation among ovarian cancer, endometriosis and PCOS: A review. *Critical Reviews in Oncology/Hematology*, *180*, 103852. https://doi.org/10.1016/j.critrevonc.2022.103852
50. Wade, M. A., Jones, D., Wilson, L., Stockley, J., Coffey, K., Robson, C. N., & Gaughan, L. (2015). The histone demethylase enzyme KDM3A is a key estrogen receptor regulator in breast cancer. *Nucleic Acids Research*, *43*(1), 196–207. https://doi.org/10.1093/nar/gku1298
51. Wang, N., Ma, T., & Yu, B. (2023). Targeting epigenetic regulators to overcome drug resistance in cancers. *Signal Transduction and Targeted Therapy*, *8*(1), Article 1. https://doi.org/10.1038/s41392-023-01341-7
52. Wang, X., Du, Z., Xu, T., Wang, X., Li, W., Gao, J., Li, J., & Zhu, H. (2021). HIF-1α Is a Rational Target for Future Ovarian Cancer Therapies. *Frontiers in Oncology*, *11*, 785111. https://doi.org/10.3389/fonc.2021.785111
53. Wilson, S., Fan, L., Sahgal, N., Qi, J., & Filipp, F. V. (2017). The histone demethylase KDM3A regulates the transcriptional program of the androgen receptor in prostate cancer cells. *Oncotarget*, *8*(18), 30328–30343. https://doi.org/10.18632/oncotarget.15681

54. Yamane, K., Toumazou, C., Tsukada, Y., Erdjument-Bromage, H., Tempst, P., Wong, J., & Zhang, Y. (2006). JHDM2A, a JmjC-containing H3K9 demethylase, facilitates transcription activation by androgen receptor. *Cell*, *125*(3), 483–495. https://doi.org/10.1016/j.cell.2006.03.027
55. Yang, Q., Yang, Y., Zhou, N., Tang, K., Lau, W. B., Lau, B., Wang, W., Xu, L., Yang, Z., Huang, S., Wang, X., Yi, T., Zhao, X., Wei, Y., Wang, H., Zhao, L., & Zhou, S. (2018). Epigenetics in ovarian cancer: Premise, properties, and perspectives. *Molecular Cancer*, *17*(1), 109. https://doi.org/10.1186/s12943-018-0855-4
56. Yoo, J., Jeon, Y. H., Cho, H. Y., Lee, S. W., Kim, G. W., Lee, D. H., & Kwon, S. H. (2020). Advances in Histone Demethylase KDM3A as a Cancer Therapeutic Target. *Cancers*, *12*(5), 1098. https://doi.org/10.3390/cancers12051098
57. Zafari Zangeneh, F., Naghizadeh, M. M., & Masoumi, M. (2017). Polycystic ovary syndrome and circulating inflammatory markers. *International Journal of Reproductive Biomedicine*, *15*(6), 375–382.
58. Zhan, M., Wen, F., Liu, L., Chen, Z., Wei, H., & Zhou, H. (2016). JMJD1A promotes tumorigenesis and forms a feedback loop with EZH2/let-7c in NSCLC cells. *Tumour Biology: The Journal of the International Society for Oncodevelopmental Biology and Medicine*, *37*(8), 11237–11247. https://doi.org/10.1007/s13277-016-4999-9
59. Zhang, H., Yang, Q., Lian, X., Jiang, P., & Cui, J. (2019). Hypoxia-Inducible Factor-1α (HIF-1α) Promotes Hypoxia-Induced Invasion and Metastasis in Ovarian Cancer by Targeting Matrix Metallopeptidase 13 (MMP13). *Medical Science Monitor : International Medical Journal of Experimental and Clinical Research*, *25*, 7202–7208. https://doi.org/10.12659/MSM.916886
60. Zhang, S., Dolgalev, I., Zhang, T., Ran, H., Levine, D. A., & Neel, B. G. (2019). Both fallopian tube and ovarian surface epithelium are cells-of-origin for high-grade serous ovarian carcinoma. *Nature Communications*, *10*(1), Article 1. https://doi.org/10.1038/s41467-019-13116-2
61. Zhou, J., Wang, Y., Wu, D., Wang, S., Chen, Z., Xiang, S., & Chan, F. L. (2021). Orphan nuclear receptors as regulators of intratumoral androgen biosynthesis in castration-resistant prostate cancer. *Oncogene*, *40*(15), 2625–2634. https://doi.org/10.1038/s41388-021-01737-1