Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

A Review on the Relationship Between p53 Gene and Viruses in Endometriosis

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Abstract. Ten percent of pre-menopausal women suffer from endometriosis which manifests as a chronic inflammatory disorder due to complicated and poorly understood pathogenesis. The relationship between P53 tumor suppressor genes and viral infections as causes of endometriosis needs complete evaluation in research. Studies conducted at the molecular level reveal endometriotic lesions display major P53 expression variations while functional regulation and defensive abilities change from somatic mutations and DNA polymorphisms in addition to epigenetic influences that block tumor-suppression operations. Multiple investigations have established that endometriotic tissues carry human papillomavirus (HPV) Epstein-Barr virus (EBV) and cytomegalovirus (HCMV) viral DNA sequences with varying frequency percentages. The proposed mechanisms study how viral oncoproteins activate P53 pathways in endometriosis development by damaging cell death systems and through their influence on inflammatory processes and genomic instability creation and cell motility changes. The review examines how such biological interactions impact endometriosis diagnosis and treatment options. Currently missing components of known analysis become apparent in this research as it points out needed study techniques for understanding the sophisticated relationship between sun-induced skin damage and Human Papillomavirus infections.

Highlights:

1. Endometriosis involves disrupted P53 function due to mutations, polymorphisms, and epigenetics.
2. Viral DNA from HPV, EBV, and HCMV is found in endometriotic tissues, implicating infections in disease progression.
3. Viral oncoproteins may alter P53 pathways, affecting inflammation, cell death, and genomic stability.

Keywords: Endometriosis, P53 Tumor Suppressor, Human Papillomavirus, Viral Oncoproteins, Inflammation

Introduction

Patients with endometriosis display endometrial tissue outside the uterus that mostly affects pelvic peritoneum together with ovaries and rectovaginal septum. Endometriosis as an estrogen-dependent disorder affects 176 million women across the

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

globe and exists in a prevalence range of 5-10% among women of reproductive age. Endometriosis presents among diverse clinical situations whereby symptom severity ranges from no symptoms to extreme pelvic pain together with menstrual cramps and intercourse-related pain and infertility complications. Endometriosis imposes a high economic strain on healthcare systems throughout the United States where researchers determine the annual expenses amount to $69.4 billion because of direct healthcare expenses alongside productivity-related indirect costs. Endometriosis rarely receives proper diagnosis although it affects many people because it takes 7-12 years for medical professionals to reach confirmation based on symptoms[1]. The waiting period for an accurate endometriosis diagnosis takes such long because patients experience normal pelvic pain symptoms while doctors assess symptoms with other diseases and only surgery can confirm the diagnosis. The detection of reliable non-invasive diagnostic biomarkers for endometriosis becomes vital because laparoscopic examination with histological confirmation remains the standard method of diagnosis today. Current endometriosis treatment mainly consists of lesion removal surgery or hormonal suppression together with surgical excision of endometrial tissue. Many patients gain symptomatic relief through these treatment approaches although they result in frequent return of symptoms alongside various side effects that affect women planning to become pregnant. The current therapeutic scenario reinforces why scientists must better understand endometriosis pathophysiology because it enables the development of new targeted treatments[2].

1. Theories of Endometriosis Pathogenesis

Although many researchers have focused on studying endometriosis multiple theories still fail to explain its true origins completely. Multiple ideas have been introduced to understand the complex physical origin of this disorder. A revision of retrograde menstruation emerged when Sampson published his theory in 1927 which is today recognized as one of the possible causes. The viable endometrial tissue that appear during menstruation is believed to create ectopic tissue before finding peritoneal attachments that allow its return to the fallopian tubes. Another hypothesis shows these processes take place at the same time. The high prevalence of retrograde

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ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

menstruation in menstruating women at 76-90% disproves its sole association with endometriosis since the condition affects only 10% of women with this condition. A different hypothesis called coelomic metaplasia exists within the medical field. Based on research evidence mesothelial cells within the peritoneum possess a capacity to transform into endometrial-like tissues under specific hormonal or inflammatory exposure. The theory addresses endometriosis occurrences in atypical areas and male cases which are extremely rare[3]. Stem cell significance drew attention through recent research findings. Studies show that stem cells which either come from bone marrow or endometrial basalis layer move beyond their typical location to develop tissue with endometrial-like characteristics. The immunological dysfunction concept describes how deficient immune surveillance enables endometrial cells to survive away from clearance by the immune system so they can easily establish and multiply in wrong locations. Endometriosis shows numerous pathological aspects which make it related to cancers. The disease develops through four significant pathological characteristics that involve invasion of local tissues while simultaneously developing new blood vessels and obstructing cell death programs. The "benign metastasising" syndrome shows genetic and epigenetic modifications identical to what is observed in cancer diseases. The cellular changes from tumour suppressor gene mutations combine with oncogene activation and damaged DNA repair systems and erratic cell cycle patterns. Discussed similarities between the diseases have generated new research about molecular mechanisms traditionally associated with cancer development. The research studied P53 as the primary tumor suppressor protein because it controls cell cycle dynamics and supports genomic stability [4].

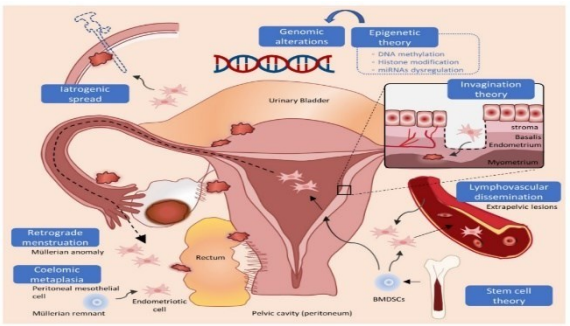

Figure 1. Theories of Endometriosis Pathogenesis: A Comprehensive Overview [5]

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2. P53 Gene: Structure and Function

Researchers continue to investigate endometriosis pathology although its original cause remains unidentified because scientists do not know the exact origin. The retrograde menstruation theory fails to fully account for endometriosis development since endometrium fragments passing backward through fallopian tubes do not necessarily lead to symptomatic ectopic growth. The stem cell theory suggests progenitor cells migrate from their source to create ectopic endometrial tissue while according to the immunological dysfunction theory reduced immune surveillance allows such ectopic growth as shown in Figure 1 [5]. The disease manifestations of endometriosis exhibit similarities with malignancies due to local invasion together with distant implantation and neoangiogenesis and resistance to apoptosis. The genome-guarding gene P53 functions as an important genetic element in these processes. The P53 gene exists at chromosome 17p13.1 which regulates cell cycle arrests and DNA repair and apoptotic responses and metabolic functions through divided functional areas. Under stress conditions P53 reaches its stable state before it becomes activated to initiate protective target genes for genomic integrity. Studies show that P53 dysregulation creates cancer cells and promotes endometriosis progression which suggests P53 could function as both a disease causes and treatment possibility [6].

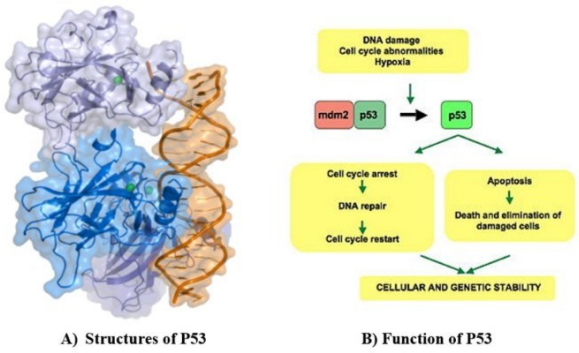

Figure 2. Structure and Function of p53.

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3. Viruses and Their Potential Role in Gynecological Diseases

Numerous gynecological disorders develop due to the involvement of infectious agents with viruses playing a significant role among them. HPV stands as a definite risk factor for cervical cancer together with anogenital malignancies because high-risk HPV types (particularly HPV-16 and HPV-18) act as carcinogenic factors in cervical cancer development. Beyond established oncogenic roles, emerging evidence suggests potential viral contributions to conditions including polycystic ovary syndrome, premature ovarian failure, and pelvic inflammatory disease.Viruses employ sophisticated mechanisms to subvert host cellular machinery for their replication and persistence as shown in figure 2 [7].Many oncogenic viruses directly target tumor suppressor pathways, particularly P53 networks, as a fundamental strategy for creating cellular environments conducive to viral replication. The E6 protein from High-risk HPV sends P53 to proteasome degradation through ubiquitin activation while Epstein-Barr virus (EBV) nuclear antigen 3C (EBNA3C) prevents both P53-mediated transcriptional expression and apoptosis. The immediate-early protein IE2-86 of cytomegalovirus acts to bind P53 which in turn prevents its ability to activate transcription. The same viral-network relations that scientists have studied extensively for their cancer effects also affect benign tissue proliferations including endometriosis. Research into disease pathogenesis of endometriosis has intensified after detecting viral sequences in endometriotic tissues because this discovery revealed their potential contribution to critical cellular pathways such as P53 networks[8].

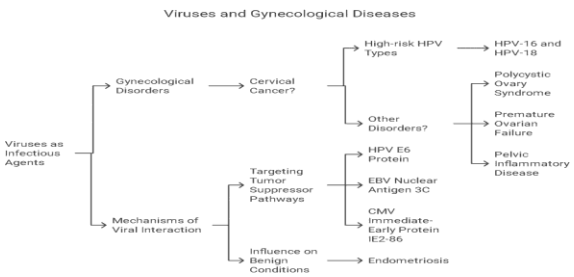

Figure 3. Viruses as Infectious Agents in Gynecological Diseases: Mechanisms and Associations (creating by researcher).

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4. Scope and Objectives of the Review

This extensive paper evaluates viral infections in endometriosis pathophysiology through analysis of its multiple facets to scrutinize previous studies. The study examines the complete collection of molecular evidence about P53 regulation in endometriotic lesions which influences expression levels and functions. Researchers assess existing studies on viral detections in endometriotic tissues by analyzing investigative methods and possible viral-induced mechanisms. Viral components play a role in endometriosis development because they relate to P53 signaling pathway alterations as shown figure 3. The research investigates the clinical impact of these interactions through examination of their relationships with disease characteristics together with malignant transformation risks and treatment possibilities. The review wraps up with two sections which address remaining questions about endometriosis research before presenting future methodologies. A review of endometriosis pathophysiology and P53-virus interactions aggregates scientific evidence toward developing molecular frameworks that serve dual requirements for new therapy development as well as translational research.

Methodology

The methodology of this review is grounded in an extensive and systematic examination of peer-reviewed scientific literature concerning the interplay between the P53 tumor suppressor gene and viral infections in the pathogenesis of endometriosis. The data was collected through a comprehensive search of biomedical databases, including PubMed, Scopus, and Web of Science, using key terms such as "P53," "endometriosis," "HPV," "Epstein-Barr virus," "cytomegalovirus," and "viral oncoproteins." Priority was given to studies published within the last fifteen years to ensure the inclusion of the most recent molecular and clinical findings. Literature was selected based on relevance to P53 expression and function, evidence of viral presence in endometriotic tissues, and proposed mechanisms of viral interference in cellular processes relevant to endometriosis development. Critical evaluation included studies employing various molecular detection techniques such as immunohistochemistry, PCR, next-generation sequencing, and in situ hybridization. Data synthesis focused on identifying consistent

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patterns of P53 dysregulation, epigenetic modifications, and correlations with clinical parameters and lesion types. Viral detection studies were analyzed in terms of virus type, localization within tissue, and the specific pathways affected. Emphasis was placed on reports providing mechanistic insights into how viral proteins interact with P53 or modulate its regulatory network. The review also incorporated epidemiological data and case-control study findings that support or challenge the association between viral agents and endometriosis risk. Collectively, this methodological approach enabled a multi-dimensional understanding of the molecular crosstalk between viral factors and the P53 pathway in the context of endometriosis.

Result and Discussion

A. P53 Aberrations in Endometriosis

1. P53 Expression Patterns in Endometriotic Lesions

Different P53 expression results from immunohistochemical assessments of endometriosis stem from multiple factors including research methods and which antibodies and tissue types were assessed as well as interpretation guidelines. Multiple patterns have been identified during the systematic analysis of these studies according to research as shown in figure 4 [9]

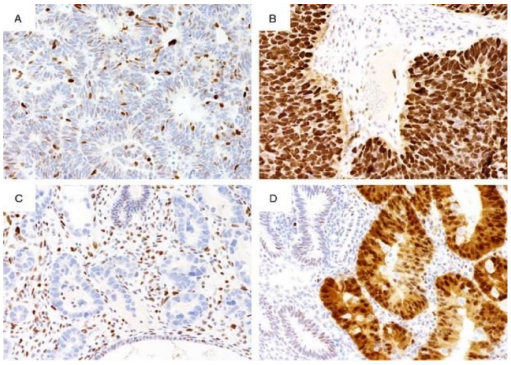

Figure 4. Patterns of p53 Expression in Endometrial Lesions – (A) Wild-type with variable nuclear staining, (B) Overexpression with strong diffuse nuclear staining, (C) Complete loss in serous carcinoma, (D) Cytoplasmic and nuclear staining [10].

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a. Altered P53 Protein Levels

Various studies document that endometriotic tissues express abnormal P53 proteins at different levels from regular endometrium. When assessing endometriotic lesions Sáinz de la Cuesta et al. discovered that P53 immunoreactivity reached 30-40% but deep infiltrating endometriosis displayed the most remarkable levels. This overexpression indicates the buildup of P53 conformations resembling mutant forms that have been observed to extend their half-life through standard immunohistochemistry methods because wild-type P53 normally turns over within 20 minutes. Different endometriotic lesions exhibit unique patterns for P53 expression according to research. Peritoneal implants showed the lowest P53 positivity rate of 21% but ovarian endometriomas demonstrated 48% positivity and deep infiltrating endometriosis displayed intermediate involvement at 32% according to Nezhat et al. Different pathogenic processes together with varying cellular origins seem to exist among distinct endometriotic lesion types. Numerous studies have recorded different P53 protein levels between the endometrial tissue and stromal components located within endometriotic lesions. Research by Govatati et al. revealed that P53 protein expression occurred most frequently in ovarian endometrioma epithelial cells with a rate of 56% while finding lower expression in the stromal components at 27% [11]. Cellular responses to the ectopic microenvironment and molecular transformation susceptibility rates differ between specific tissue areas according to expression patterns [11].

b. Correlation with Clinical Parameters

Different clinical parameters show correlations with P53 expression levels found in endometriotic tissues. Multiple research findings show P53 immunoreactivity leads to more severe disease conditions according to revised American Fertility Society (rAFS) criteria while stage III and IV diseases show higher protein expression. Various research studies observed P53 expression directly linked to dysmenorrhea pain symptoms and other pain symptoms. Available research shows P53 immunoreactivity shows periodic changes

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between the proliferative and secretory menstrual phases. The cyclic variations in P53 expression parallel hormonal influence on this protein which supports the estrogen-dependent nature of endometriosis[12].

c. Relationship with Proliferation and Apoptosis

Multiple research studies have confirmed relationships that exist between P53 protein levels and measures of cellular growth rate and cell death in endometriotic tissue samples. Scientists found that P53 protein immunoreactivity exhibited positively correlated results with Ki-67 proliferation index across endometrium tissue samples from both affected sites of endometriosis patients indicating possible proliferative effects of accumulated P53 protein. The detection of P53 protein inversely related to apoptotic activity ratings has been reported within endometriotic lesions indicating potential anti-apoptotic properties. Studies suggest that newly synthesized P53 mutant proteins may work as dominant negative factors through their ability to combine with wild-type P53 proteins to block normal P53 activity thereby leading to resistance against cell death even with visible protein levels detectable in tests[13]

2. TP53 Genetic Alterations in Endometriosis

Somatic TP53 mutations appear infrequently in endometriosis since these mutations are observed in only less than 50% of cases of high-grade serous ovarian cancer. The direct sequencing of TP53 exons that focus on hotspots in exons 5-8 reveals mutations occur below 10% in frequency. Next-generation sequencing techniques demonstrate that 20-25% of endometriotic lesions show low-frequency TP53 mutations when assessed for next-generation sequencing. These cases usually have atypical features or neighbor endometriosis-associated ovarian carcinomas. These findings suggest that TP53 mutations may occur in a subset of lesions with premalignant potential or undergoing malignant transformation[14]. Unlike the mutation patterns in gynecological cancers, endometriosis predominantly exhibits missense mutations in the DNA-binding domain rather than nonsense or frameshift mutations, possibly indicating distinct

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selective pressures in benign versus malignant conditions, where gain-of-function or dominant-negative mutations may provide a survival advantage to endometriotic cells. Research shows that endometriotic tissues tend to develop Loss of heterozygosity (LOH) at TP53 locus (17p13) but this specific genetic alteration occurs most frequently in ovarian endometriomas. Laboratory evidence has identified TP53 LOH occurring between 25 and 75% of cases in endometriotic cysts but the highest frequencies emerge when studying lesions near ovarian carcinomas associated with endometriosis. TP53 loss and other tumor suppressor locus defects appear early during the evolution of malignant endometriosis with special prevalence in endometriotic ovarian cysts that will frequently develop clear cell and endometrioid ovarian carcinomas[15]. Rephrased scientific data shows LOH first occurs at TP53 before mutational onsets indicating typical endometriosis progression toward atypical forms and cancer. Among the TP53 polymorphisms examined for endometriosis risk susceptibility stands the rs1042522 polymorphism that leads to production of arginine (Arg) or proline (Pro) at the 72nd residue. Cells with the Arg72 variant present better apoptotic capability because their mitochondria effectively localize with pro-apoptotic factors but cells with Pro72 resist apoptosis better which allows these cells and endometrial lesions to persist. Research involving 12 case-control studies demonstrated that Asian people with the Pro/Pro genotype faced elevated endometriosis risk (OR=1.61, 95% CI: 1.10-2.35) but Caucasian populations did not show the same pattern. This indicated population-specific genetic risk factors between Asian and Caucasian groups. The Arg72 variant displays seven times greater proteolytic sensitivity to HPV E6 oncoprotein than the Pro72 variant thus affecting both HPV-based endometriosis likelihood and disease course. Research studies found conflicting results regarding how endometriosis risk relates to two TP53 polymorphisms known as rs17878362 and rs1625895 which affect TP53 mRNA stability and protein expression regulation as shown in figure 5 [16]

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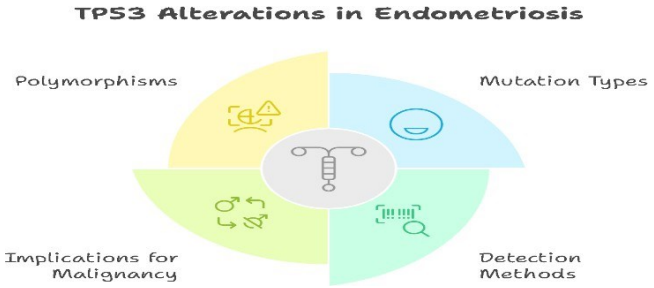

Figure 5. TP53 Alterations in Endometriosis – Polymorphisms, Mutation Types, Detection Methods, and Malignancy Implications(creating by researcher).

3. Epigenetic Regulation of P53 in Endometriosis

The study shows DNA methylation abnormalities create endometriosis-related gene suppression by allowing 30-40% TP53 promoter methylation in endometriotic tissues when normal endometrium has 5% or less. A decrease in P53 mRNA expression occurs because DNA epigenetic modification acts independently from genetic mutations during hypermethylation. TP53 methylation affects endometriosis types with deep infiltrating endometriosis showing the highest frequency and peritoneal lesions exhibiting the lowest rate thus influencing deep infiltrating lesions' invasive characteristics. Medical research demonstrates that endometriotic stromal cells become responsive to P53 expression after treatment with DNA methyltransferase inhibitor 5-aza-2'-deoxycytidine because this reduces both proliferative cell behavior and invasive capabilities. MicroRNAs (miRNAs) control the post-transcriptional P53 pathway during Endometriosis developmental stages. Different miRNAs that control P53 signaling pathway expression or its regulatory elements demonstrate alterations in endometriotic tissue samples. The increase of miR-125b levels triggers post-transcriptional silencing by degrading P53 mRNA to reduce protein abundance. A reduction in miR-34 family members expression impairs P53-mediated apoptosis and senescence because P53 forms a positive regulatory loop with these miRNAs[17]. The suppression of miR-145 (MDM4 inhibitor) and miR-542-3p (MDM2 inhibitor) causes degradation of P53 through reduced inhibitory regulation without affecting transcription levels. The pattern explains why there may be differences in the amounts of mRNA and protein when examined separately. The regulatory pathways go through alterations which modify the P53 pathway during endometriosis progression. Endometriosis patients exhibit significant MDM2 overexpression in their eutopic and ectopic endometrium tissue which accelerates P53 degradation thus decreasing P53 tumor-suppressive activity although no TP53 mutations are present. Some populations demonstrate increased endometriosis risks when the MDM2 SNP309 T>G polymorphism occurs because this genotype establishes a new SP1 binding site that drives higher

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MDM2 expression. A weakened P53 tumor-suppressive role results from the endometriotic tissue reduction of positive regulator ARF (p14ARF) together with increased MDM2-mediated degradation which ARF normally inhibits. The transcriptional activities of P53 become dysfunctional in endometriosis because P53 target gene expression displays alterations that weaken regulatory function. Although P53 proteins can be detected in endometriotic lesions p21 (CDKN1A) shows decreased expression as a primary P53-mediated cell cycle arrest inhibitor. The endometriotic cells demonstrate decreased expression of pro-apoptotic P53 target BAX compared to the anti-apoptotic BCL-2 gene which creates unfavorable conditions leading to apoptotic resistance. Endometriotic cells remain alive and multiply outside the normal locations even though stress signals should activate P53-dependent apoptotic cell death mechanisms. Among P53 apoptotic regulators PUMA and NOXA show diminished expression patterns during examinations of endometriotic stromal cells when compared with normal endometrial stromal cells. The pathogenesis of endometriosis is strengthened by these alterations which help endometriotic cells to survive and establish in ectopic locations as shown in figure 6 [18].

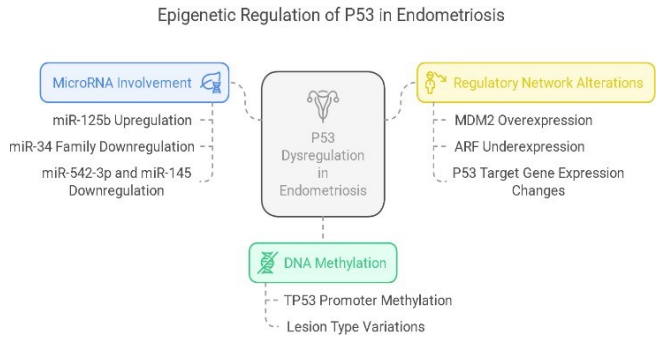

Figure 6. Epigenetic Regulation of P53 in Endometriosis – MicroRNA, DNA Methylation, and Regulatory Network Alterations (creating by researcher).

B. Viral Infections in Endometriosis

1. Evidence for Viral Presence in Endometriotic Tissues

Research has evaluated viral involvement in endometriosis development but different studies report varying detection results for multiple pathogens. Science confirms Human Papillomavirus (HPV) exists in endometriotic tissues based on studies which document a broad detection rate between 0% and 35%. The primary cause of this variation stems from dissimilarities in detection strategies and sampling procedures and geographical location differences. PCR detection methods report higher pathological outcomes than in situ hybridisation and

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

immunohistochemistry therefore providing more trustworthy results. The PCR technique shows higher efficiency than other methods so it leads to these results. HPV-16 and HPV-18 stand as the two primary virus types among all high-risk human papillomavirus (HPV) cases[19]. Research studies have shown that HPV rates differ significantly between samples from endometriosis patients compared to normal endometrial samples. Multiple reasons exist that explain the noted variations between assemblage samples. The collection process of samples sometimes leads to negative outcomes discovered by various studies specifically the contamination risk that starts within the lower vaginal canal. The presence of these problems creates a need to investigate human papillomavirus (HPV) as a possible contributor to endometriosis pathophysiology. The evidence reveals that the discovery of particular positive results could result from procedural contamination rather than authentic disease. The lower detection rates in samples collected transabdominally explain this situation.

Endometriotic lesion identification shows better reliability through Epstein-Barr Virus (EBV) testing than human papillomavirus (HPV) testing according to scientific research. EBV DNA appears in a higher amount in endometriotic lesions than the amount found in typical endometrial tissue since 76.2% of endometriotic lesions contain EBV DNA yet only 15% of typical endometrial samples have EBV DNA present. Research using in situ hybridization demonstrated that EBV transcripts transfer to epithelial cells found in endometriotic lesions thus proving the virus's actual presence. Scientific evidence shows deep infiltrating endometriosis contains endometrial bacterial vaginosis in 52% of cases while peritoneal lesions present in 31% and ovarian endometriomas show the condition in only 22% of cases[20]. The invasive characteristics of different kinds of lesions become evident through this finding. Lab tests have confirmed that endometriotic tissue cells present EBV oncoprotein LMP1 that activates signaling pathways leading to malignancy. Studies indicate such oncoproteins are associated with invasiveness markers such as MMP-9 which leads to disease progression. Medical researchers identified Human cytomegalovirus (HCMV) in 16.5% of endometriotic lesions yet only 4.0% of control specimen expressed viral proteins. No viral protein expression was detected in the control samples whereas the expression remained absent showing a distinct pattern. Most viral protein expression occurs within the glandular epithelium according to current observations. A large number of studies show HCMV absence in evaluation groups and their disparate research results contradict each other. The research teams published these results in their published works. The different methods used for selecting PCR primers together with DNA preservation methods and detection sensitivity approaches result in these inconsistent findings. Research carried out in test tubes shows HCMV establishes productive cell infections inside endometrial cells regardless of the ongoing experimental variations [21]. Angiogenic and inflammatory changes from the

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infection may substantially contribute to the pathophysiology of endometriosis. Scientific studies show endometriotic lesions contain various viruses among them the polyomaviruses which include BK and JC viruses. Research shows that the BK virus appeared more frequently than the JC virus because it infected 28.1% of samples while the JC virus infected only 12.5% of the cases. The persistent infections of reproductive organs by viruses are possible through their T-antigens and these viruses alter pathways which protect against tumors. The research regarding the presence of herpes simplex virus types 1 and 2 (HSV-1/2) in samples has proven inadequate and yielded no significant results. The identification of the virus continues despite possible lab-based limitations connected with finding it. Certain studies have shown that human endogenous retroviruses called HERVs show abnormal patterns of expression inside endometriotic tissues. Researchers have observed high levels of the HERV-K envelope protein in the endometrium tissues during investigation. This protein exists at elevated levels in all areas of endometrium tissue including ectopic and eutopic regions. The inflammatory conditions seen in endometriosis might stem from changes to this particular retrovirus. This is likely the situation as shown in figure 7 [22].

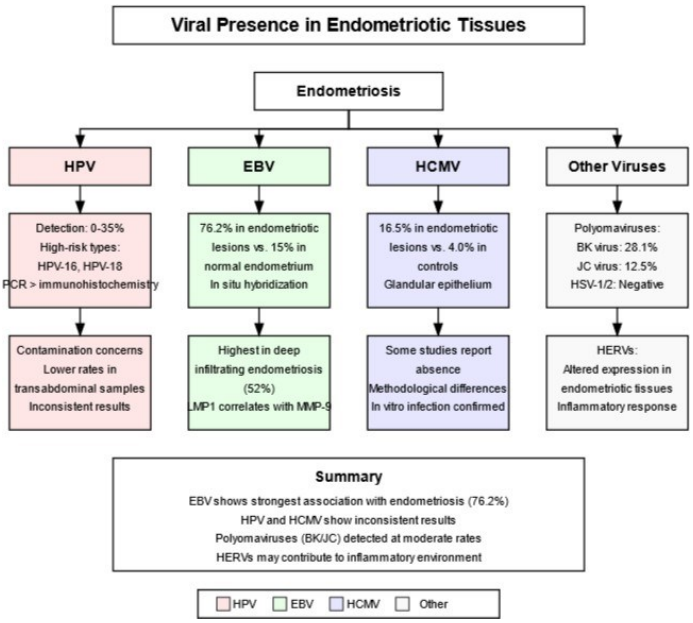

Figure 7. Viral Presence in Endometriotic Tissues: Prevalence, Detection Methods, and Potential Role in Disease Pathogenesis(creating by researcher).

2. Mechanisms of Viral Contribution to Endometriosis

The process of endometriosis development is possibly caused by viruses which utilize direct cellular transformation and inflammatory modulation and immune

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dysregulation in addition to epigenetic reprogramming as well as oxidative stress induction. VP16 E6 and

E7 from HPV along with EBV LMP1 protein and polyomavirus T-antigens transform endometrial cells directly. The HPV-16 E6/E7 proteins increase cellular growth along with movement and cell penetration activities by disrupting P53 and pRb tumor control molecules and triggering telomerase activation and causing genomic disorders in cell systems. The EBV protein LMP1 induces epithelial-mesenchymal transition (EMT) by elevating the activity of NF-κB as well as MAPK while stimulating MMPs and VEGF release together with COX-2 enhancement which hastens endometriosis disease progression. HCMV infection of cells promotes the release of pro-inflammatory cytokines including IL-1β and TNF-α and IL-6 together with angiogenic factors VEGF and IL-8 and prostaglandins which produce an inflammatory state similar to endometriotic lesions. The survival rates of cells infected by HCMV improve under hypoxic scenarios which helps implantation of endometriotic tissues prior to vessel development. Viral infections lead to inflammatory modulation that contributes to chronic inflammation which defines endometriosis as a disease. Cellular pattern recognition receptor activation through TLRs and RLRs leads to NF-κB and IRF activation and subsequently boosts cell survival factors together with proliferation strengths and draws immune cells into the affected area. The combination of HPV E6 and HCMV IE1 proteins unleashes COX-2 gene activation that leads to elevated prostaglandin E2 (PGE2) levels thus improving vasodilation and vascular permeability and immune system modifications which sustain endometriotic lesion survival[23]. Endometriosis triggered immune dysregulation develops from three distinct elements involving altered NK cell performance and abnormal macrophage actions and misregulated Th1/Th2 cell pathways. The immunosuppressive proteins from EBV that contain BCRF1 use viral IL-10 homolog activity to suppress NK cells and decrease Th1 cell response capability. Endometriosis weakens NK cell cytotoxic abilities resulting in the inability to eliminate ectopic endometrial cells and subsequently their survival. Endometriosis causes comparable changes to the immune system like those which occur during EBV and HCMV infection. HCMV produces multiple immune-modulating proteins composed of US2 along with US3, US6, and US11 and pairs them with UL144 and viral chemokines UL146, UL147, US28 and NK cell inhibitory proteins UL18, UL40 to establish endometriotic implant immune tolerance. Endometriotic cells maintain HPV survival through E5, E6 and E7 proteins that lower MHC class I expression levels and stop interferon signals and modify antigen-presenting cell functionality. Endometriosis pathology shows most of its epigenetic modifications because of viral involvement in epigenetic reprogramming. HPV E7 protein activates DNA methylation regulators DNMTs and histone deacetylases HDACs to change DNA modifications and repress tumor suppressors while disabling hormone receptors[24]. Infectious EBV causes elevated expression of DNMT1 and

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DNMT3A along with DNMT3B that creates excessive methylation of tumor suppressors HOXA10, PR-B and E-cadherin in endometriotic tissues. The HCMV immune-early proteins interact with histone-modifying enzymes to reorganize chromatin structure that results in genetic expression modifications which potentially affect steroid hormone actions and cell-binding along with inflammatory response processes. The pathophysiology of endometriosis shows reactive oxygen species (ROS) production as an essential factor through oxidative stress because viral infections create such conditions. Endometriotic tissues show elevated lipid oxidative markers alongside diminished antioxidant capabilities that leads to DNA damage together with EMT activation and inflammatory reaction. urvival protein GSTP1 becomes a target for HPV E6 which causes its breakdown leading to diminished antioxidant capacity and resulting cell damage. The pathogen HCMV disrupts mitochondrial electron transport by means of UL37x1 proteins to generate excessive ROS that causes both DNA damage and inflammatory reactions and genomic instability. Through oxidative stress NF-κB activation forms a cycle that boosts both ROS levels and inflammatory cytokines production and leads to endometriosis progression as established in published research as shown in figure 8 [25].

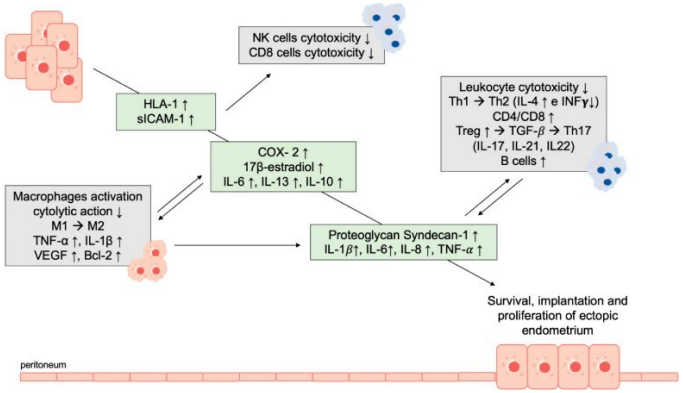

Figure 8. Immune Dysregulation and Inflammatory Pathways in Viral Contribution to Endometriosis[26]

C. P53-Virus Interactions in Endometriosis

The cancer-causing viruses use complex mechanisms to keep P53 protein inactive so cellular conditions become advantageous for their reproduction. The pathophysiological processes of endometriosis might be affected by cellular pathways which alter genomic instability and cell survival and cell proliferation. The high-risk HPV E6 proteins together with E6-associated protein (E6AP) and P53 form a trimeric complex in solution. The trimeric complex results in P53 getting marked for ubiquitination before its subsequent proteasomal destruction. The tumor-suppressing functions of P53 gene result in the development of genomic instability

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

and resistance to programmed cell death known as apoptosis. The quantities of P53 protein decrease through post-translational degradation in HPV-positive endometriotic lesions while P53 mRNA levels stay normal. HPV plays an essential role in maintaining endometriosis lesions because the survival rate of endometriotic cells increases alongside higher cell generation frequencies and diminishing cell mortality rates. The TP53 codon 72 polymorphism potentially affects how the body reacts to HPV-associated endometriosis. The Arg72 homozygous variation shows higher sensitivity toward E6-mediated protein breakdown. Multiple proteins which modify P53 functional properties originate from EBV genetic material. Through activation of NF-κB by LMP1 the pathway activates production of ΔNp73 to lower P53 transcriptional activity [27]. Research indicates P53 immunoreactivity presence alone may not explain why P53 loses its ability to restrict tumour growth. 'nun function of MDM2 but also causes it to become hyper-phosphorylated thus leading to reduced P53 transcriptional activity.. The processes that have been explained above result in the suppression of P53 in endometriotic lesions that are positive for EBV. This suppression allows for uncontrolled cell proliferation as well as escape from immune responses. HCMV is responsible for the encoding of several proteins that disrupt the function of P53. IE2-86, an early protein, is responsible for the expression of this molecule, which inhibits the DNA binding ability of P53 and suppresses its gene transcription without altering the amount of protein it produces. Lesions of the endometrium that are positive for HCMV may have accumulating P53, despite the fact that the protein continues to be useless. Cell cycle progression is driven by the HCMV pp71 protein, which causes Rb to be destroyed by proteasomes, which in turn leads to aberrant P53 regulation and ultimately drives cell cycle progression. The DNA polymerase processivity factor UL44 prevents P53 from adhering to target gene promoters, which results in an increase in the degree to which P53 actions are inhibited. During the interaction between the Polyomavirus large T-antigens and the DNA-binding domain of P53, the DNA-binding domain of P53 becomes inoperable while maintaining its stability [28]. The accumulation of the P53 without any performable function is caused by an infection with the BK virus, which brings about malfunctions that are similar to those that are observed in polyomavirus-associated malignancies and endometriotic illnesses. The function of pRb is disrupted by the large T-antigen that is produced by the BK virus, which makes the sequence of cell cycle dysregulation much more severe. When these elements interact with one another, endometriotic cells have the ability to obtain benefits that allow them to survive and proliferate. P53 activity shows evidence of viral modulation in addition to the direct virus targeting that it demonstrates. It is via the disruption of upstream regulators that the mechanisms function, which is then followed by the alterations that take place after translation. It has been shown via experiments that the HPV E7 virus, in conjunction with the HCMV pp71 virus, will activate MDM2 in order to destroy P53 while simultaneously boosting its levels

Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

in human cells. In order to prevent P53 from being acetylated, other viral proteins, such as EBV BZLF1 and HCMV IE1, employ p300/CBP as their target. The quantity of the proteins do not change, but the transcriptional activity diminishes as a result of performing this procedure. HCMV UL44 and HBV HBx are responsible for rerouting the P53 protein to the cytoplasm of the cell, where it is unable to function as a tumour suppressor in the nucleus of the cell. HPV E6 is responsible for the degradation of TIP60, which is a histone acetyltransferase that is necessary for P53-dependent apoptosis. This results in an increase in the apoptotic resistance of endometriotic cells. The viral ways that assault P53 play a crucial role in both the maintenance and proliferation of ectopic endometrial lesions. Additionally, these viral methods have the potential to elude immunity, which reinforces the connection between viral infections and the development of endometriosis as shown in figure 9 [29].

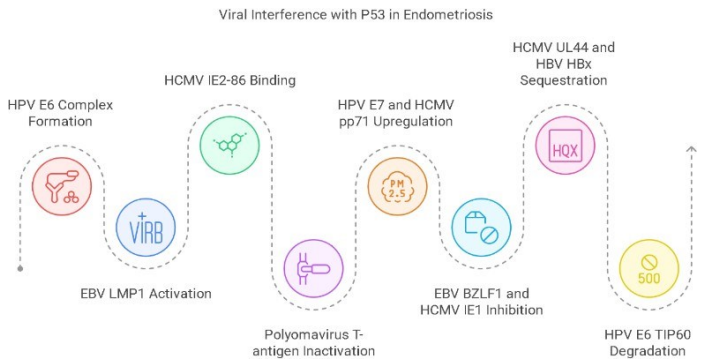

Figure 9. Viral Interference with P53 in Endometriosis (creating by researcher).

1. Cooperative Effects on Cellular Processes

The cells in endometriosis possess significant genomic instability expressed through chromosomal abnormalities and microsatellite instability and DNA damage indicators. The markers show effects from P53 deficiency together with viral infections. P53 normally coordinates all cellular activities that happen after DNA damage identification. The cellular response can activate repair mechanisms while severe cases trigger apoptosis to proceed. The decreased functional state of P53 allows genetic abnormalities to build up that increases both illness development and cancer transformation probability. Numerous mechanisms allow viruses to contribute to the instability of genetic material [30]. HPV E6/E7 proteins activate events that create abnormal centrosomes as well as mitotic errors which leads to problematic cellular divisions. The DNA repair system suffers additional damage through the action of EBV LMP1 which blocks essential processes of base excision repair. The DNA damage responses triggered by HCMV UL76 together

Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

with chromosomal breaks create more detrimental harm to genomic integrity. The polyomavirus T-antigens break down mitotic checkpoint control thus allowing injured cells to multiply autonomously [31]. Particularly in premalignant endometriotic lesions, the cumulative effects of P53 malfunction and viral interference lead to a gradual accumulation of genetic abnormalities. Such alterations serve as critical factors in disease evolution and provide possible therapeutic interventions for medical treatment. The cells involved in endometriosis demonstrate increased cell mobility and invasive traits that enables their better implantation and deeper penetration of peritoneal tissue surfaces. Fundamentally wild-type P53 prevents the migration and invasion process through its control of Rho GTPases and regulation of both epithelial-mesenchymal transition (EMT) and matrix metalloproteinases (MMPs). The three different mechanisms are exclusively responsible for stopping cellular migration and invasion. Endometriotic cells tend to display invasive behaviors due to P53 failure particularly when deep infiltrating endometriosis (DIE) occurs due to this specific mechanism. The process of cell migration and invasion receives increased acceleration from viruses through multiple recognized mechanisms. EBV LMP1 activates NF-κB signaling to generate more MMP-9 thereby leading to degradation of extracellular matrix while HPV E6/E7 proteins drive EMT marker increases which includes vimentin and N-cadherin expression. The polyomavirus small t-antigen activates Rac1 protein to advance cytoskeleton changes and cell movement efficiency [32]. Through HCMV US28 activation the STAT3-dependent mechanisms get boosted to drive cellular migration forward. The penetration of pelvic tissues causes severe symptoms and heavyweight in deep infiltrating endometriosis when acted aggressively. When P53 fails alongside these viral pathways the result becomes a highly invasive phenotype. The disease exhibits these characteristics most prominently when the condition reaches advanced stages of deep infiltration. Lesions of endometriosis require angiogenesis for survival and growth because they contain elevated levels of angiogenic factors while exhibiting elevated blood vessel density. The normal activity of P53 induces angiogenesis inhibition through VEGF transcription suppression while triggering production of anti-angiogenic thrombospondin-1. A disrupted P53 activity causes the suppression mechanism to fail thus the production of VEGF becomes elevated leading to a highly vascularized structure within the lesion. Different mechanisms enable viruses to initiate angiogenesis during their functions. HPV E6 controls HIF-1α stability to enhance VEGF transcription. Activation of NF-κB and AP-1 by EBV LMP1 creates both IL-8 and VEGF production but HCMV US28 activates angiogenic pathways producing excessive VEGF through a constant mechanism. Big T-antigen stabilizes the HIF-1α protein thereby enhancing the expression of angiogenic genes. The formation of endometriotic lesions occurs from pro-angiogenic effects caused by viruses and from P53 dysfunction leading to a

Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

vascular network that supports endometriosis development and persistent growth and results in disease progression as shown in figure 10 [33]

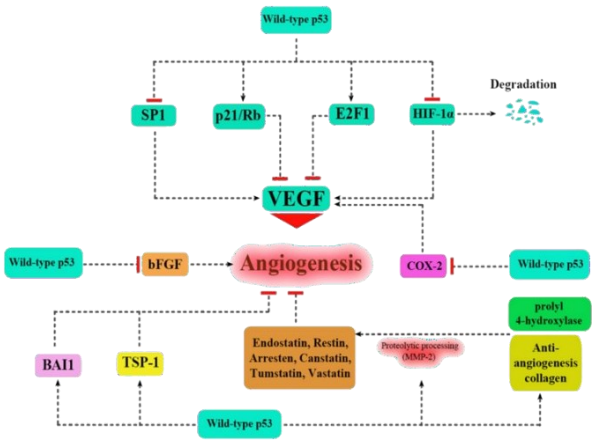

Figure 10. P53-Mediated Regulation of Angiogenesis and VEGF Pathways in Endometriosis [34]

D. Clinical Implications

The P53 alterations in combination with viral infections determine how endometriosis phenotypes develop and advance during the disease process. The three types of endometriosis lesions (peritoneal, ovarian, DIE) show different molecular patterns because of both P53 dysfunction and viral influence. Deep infiltrating endometriosis shows the most frequent P53 mutations in addition to EBV virus identification so researchers propose this combination explains its aggressive disease features. P53 deficiencies together with viral oncoproteins collaborate to control MMP expression and promote epithelial-mesenchymal transition (EMT) as well as tissue invasion thus explaining the invading behavior of these lesions[35]. Ovarian endometriomas demonstrate moderate P53 impairment together with viral infections leading to increased malignant potential because this combination promotes genetic mutations while destabilizing the genome due to missing P53 function and viral effect on DNA integrity. DNA damage together with carcinogenic potential increases when the iron-rich microenvironment of cysts interacts with viral oxidative stress mechanisms which result from repeated hemorrhage. Peritoneal endometriosis follows adhesion-based rather than invasion-driven mechanisms because it demonstrates the lowest levels of P53 dysfunction and viral presence regardless. The diagnostic value of P53 dysfunction with viral infections for endometriosis becomes clearer because this knowledge enables non-invasive testing to shorten diagnostic delays. P53 expression patterns together with viral markers possess the potential to function as disease biomarkers for detection and classification and for monitoring disease advancement[36]. To begin assessment medical specialists first conduct tests through marker analysis that requires blood

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https://doi.org/10.21070/ijhsm.v2i1.130

tests from the peripheral system alongside examination of menstrual fluid and peritoneal fluid. Medical staff depend on P53-viral signatures to determine different patient risk categories by evaluating patients with high disease progression chances to develop personalized treatment strategies. The healthcare provider network gives doctors access to pharmacodynamic indicators that track drug performance. The liquid biopsy detection system incorporates DNA circulating tests with proteomic protein evaluations and exosomal microRNA evaluation and virus-specific immunological analysis. Multiple clinical assessment levels need to confirm these methods before their implementation in broad clinical environments. The medical care advances emerging from the P53 dysfunction-viral infection link in endometriosis allow more effective treatments than the methods previously used based on hormones and surgery. Treatment success was demonstrated in anticancer therapy when PRIMA-1 and APR-246 were combined with wild-type P53 activation enabled through the use of MDM2-P53 inhibitor treatments involving nutlins and AMG-232. Research into endometriosis disease progression factors caused by viral elements may signal the development of novel therapeutic approaches for treating this condition [37]. Medical treatment of endometriosis depends on viral replication agents combined with direct-acting antivirals and immune-modulating therapies as well as therapies that focus on viral replication. Endometriosis patients who show epigenetic dysregulations receive treatment through the medicine combination of DNA methyltransferase inhibitors decitabine and azacitidine alongside histone deacetylase inhibitors vorinostat and valproic acid. Many scientific researchers look into multiple treatment approaches to control P53 destruction pathways during viral infections. When medical providers combine NF-κB inhibitors with selective COX-2 inhibitors and inflammation-reducing anti-cytokine drugs in their treatment protocols endometriosis becomes less active. The medical treatment for endometriosis offers transformative benefits because it combines assessments of P53 protein failure and viral infection effects and inflammation reactions simultaneously. Medical practitioners enhance the delivery of healthcare through molecular profiling data to design treatments that increase patient health outcomes and minimize disease relapse risks. The persistent nature of endometriosis requires complete clinical trials for proving operational safety and disease control capacity since medical professionals view it as a benign condition [38]

E. Research Challenges and Future Directions

Multiple experimental challenges prevent researchers from obtaining correct interpretations of scientific studies focusing on P53-virus interactions in endometriosis. Northeastern University has established multiple heterogeneous characteristics of endometriotic lesions that create a barrier for uniform scientific research across subjects and within subjects. The analysis of molecules faces complications from various tissue attributes that create difficulties when working

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

with bulk tissue samples. Molecular characterization needs advanced methods to connect tissue dissection operations with single-cell methods for proper entity identification. Control tissue selection plays a critical role in researcher effectiveness because proper choice allows them to better understand experimental results. Two main sources of control tissue exist: peritoneum tissue obtained from healthy individuals together with disease-free endometrium samples and endometrium from endometriosis patients who show complexities in sample acquisition [39]. Multiple methods used to conduct control implementation throughout research studies make it difficult to assess identical research findings.The detection algorithms show performance issues because they possess different detection sensitivities and precision levels. PCR-based technology delivers outstanding sensitivity but it requires users to handle both minimal viral load discoveries and lab contaminants which then affects the results of in situ Hybridization and immunohistochemistry methods and Next-generation sequencing (NGS) offers full sequence analysis yet requires complicated bioinformatics to distinguish genuine viral sequences from data background.The accuracy of research results depends on various elements that originate from sampling approaches combined with laboratory handling operations. Laboratory researchers obtain better quality nucleic acids from frozen fresh tissue than from paraffin-fixed formalin-fixed tissue but the latter is less commonly obtained.The detection validity of viruses might be endangered by sample contamination during the vaginal sampling process. The identification of cause-effect relationships stands as the greatest scientific challenge around the world during present times [40]. Research based on designed experiments and controlled clinical trials must determine the impact of P53 mutations and viral infections on the disease progression of endometriosis. Standardized protocols together with selected controls need to get implemented to supplement methodological solutions aimed at resolving these limitations. Further research into these components proves necessary since it enhances our knowledge about P53 failure together with viral infection involvement in endometriosis pathogenesis. The evaluation approach for P53-virus-endometriosis research needs to be advanced according to [41]. Scientists need to use multi-omics analysis with genomic transcriptomic proteomic and metabolomic methods for proper evaluation of identified endometriotic lesions. Molecular analysis methods enable researchers to successfully detect both viral markers with P53 dysfunction patterns because of their integrated spatial resolution features. Single cell RNA sequencing analysis along with actual laboratory work permits researchers to conduct P53-virus interaction studies in every epithelial and stromal compartment cell type while effectively maintaining tissue samples. The study of P53 and viral presence patterns in patients during treatment will help scientists understand both the disease development process and the therapeutic response along with identification of disease origins. Experts need to create advanced laboratory systems which will help them study the P53 variant protein as

Indonesian Journal on Health Science and Medicine
Vol 2 No 1 (2025): July
ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

https://doi.org/10.21070/ijhsm.v2i1.130

it interacts with viral pathogens for thorough analysis of research variables. The research must apply humanized mouse models to investigate how viruses cause endometriosis development since they sustain human viruses. The study requires an investigation of viral oncoproteins effect on P53 functional changes within endometrial and endometriotic cells followed by examination of P53 dysfunctional control impact on viral replication patterns while assessing this research for proliferation dominance and invasion power and failure of apoptosis in pathogenic endometriosis patterns. Research teams needed to conduct therapeutic tests that would confirm both treatment success metrics and multicomponent therapeutic relationships. More research trials must build innovative treatments based on P53 targeting practices and antiviral techniques to slow the disease path and minimize recurring symptoms. Better endometriosis diagnostic tools and innovative management systems can develop through methodical collaboration of scientific professionals based on P53-virus interaction knowledge.

Conclusions

The research of P53 alterations together with viral agents in endometriosis exists as a little-studied field which shapes our understanding of disease processes and therapeutic development. Numerous proof suggests endometriotic tissues contain P53 functional protein defects and viral agents but scientists need to study better how these elements generate endometriosis progression together. Research about endometriosis development from P53 and viral infection can be better understood because it reveals the mechanisms of viral oncoprotein destruction of P53 alongside the combined cellular death resistance pattern which creates genomic instability with heightened inflammatory signaling networks. Various investigation methods should explore these mechanisms to understand their role in developing endometriosis and monitoring its malignancy risk path. The examination of P53-virus interaction systems operating within endometriosis represents a substantial medical value for developing detection approaches and enhancing prediction of clinical outcomes and treatment strategies. Digging into biological pathways leads to three clinical advantages through non-invasive medical test equipment and disease risk evaluation procedures along with proper therapeutic networks that specifically target these cellular networks. Future medical solution development will succeed through research that integrates molecular evaluation methods and intervention research and basic science research models for medical applications. Research efforts from different fields unite their work to enhance

ISSN 3063-8186. Published by Universitas Muhammadiyah Sidoarjo

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endometriasis pathology comprehension and enhance care delivery for global endometriasis patients.

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