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Endocrine-immune interactions in Hashimoto's thyroiditis and human papillomavirus–induced cervical cancer: the role of Epstein-Barr, hepatitis C, and hepatitis D viruses in shared pathogenesis

Endokrino-imunološke interakcije u Hašimotovom tireoiditisu i karcinomu grlića materice indukovanom humanim papiloma virusom: uloga virusa Epstein-Barr, hepatitis C i hepatitis D u zajedničkoj patogenezi

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Abstract

Hashimoto's thyroiditis (HT) and human papillomavirus (HPV)-induced cervical cancer (CC) are distinct clinical entities; however, their etiologies share several pathogenetic mechanisms related to immune dysregulation, endocrine disturbances, and chronic inflammation. HT is an autoimmune disease characterized by lymphocytic infiltration of the thyroid gland, autoantibody production, and progressive tissue damage resulting from a persistent inflammatory response. In contrast, the development of HPV-induced CC depends on the virus's ability to evade host immune surveillance, thereby enabling long-term persistence of the infection. Increasing evidence suggests a potential role of other viral infections, particularly Epstein-Barr virus and hepatitis C virus, in the development of autoimmune thyroid diseases. The underlying mechanisms include chronic inflammation, molecular mimicry, and impaired immune tolerance. Furthermore, thyroid hormones and the sex hormones estrogen and progesterone play a significant role in modulating innate and adaptive immune responses and may influence the persistence of viral infections. Although there is an overlap in the immunological and endocrine mechanisms involved in these conditions, current evidence remains insufficient to confirm a direct association between HT and an increased risk of developing CC. Further experimental and epidemiological studies are required to elucidate the potential relationship between HT and HPV-induced CC.

Keywords:
autoimmune diseases; hashimoto disease; hepatitis viruses; human papillomavirus viruses; risk assessment; uterine cervical neoplasms.

Apstrakt

Hašimotov tireoiditis (HT) i humanim papiloma virusom (HPV)-indukovan karcinom grlića materice (*cervical cancer* – CC) različiti su klinički entiteti, ali u etiologiji obe bolesti je nekoliko zajedničkih patogenetskih mehanizama povezanih sa poremećajima imunskog i endokrinog sistema i hroničnom inflamacijom. HT je autoimunska bolest koju karakterišu limfocitna infiltracija štitaste žlezde, produkcija autoantitela i progresivno oštećenje tkiva žlezde usled perzistentnog inflamacijskog odgovora. Nasuprot tome, razvoj CC indukovanog HPV-om zavisi od sposobnosti virusa da izbegne imunološki nadzor domaćina, što omogućava dugoročnu perzistenciju infekcije. Sve više dokaza ukazuje na moguću ulogu drugih virusnih infekcija u nastanku autoimunskih bolesti štitaste žlezde, posebno Epstein-Barr-ovog virusa i virusa hepatitisa C. Osnovni mehanizmi uključuju hroničnu upalu, molekularnu mimikriju i poremećenu imunološku toleranciju. Osim toga, hormoni štitaste žlezde i polni hormoni estrogen i progesteron imaju značajnu ulogu u modulaciji urođenog i stečenog imunskog odgovora i mogu uticati na perzistenciju virusnih infekcija. Mada postoji preklapanje u imunološkim i endokrinim mehanizmima uključenim u ta stanja, trenutno nema dovoljno dokaza koji potvrđuju direktnu povezanost HT sa povišenim rizikom od nastanka CC. Potrebna su dodatna eksperimentalna i epidemiološka istraživanja, kojima bi se razjasnila potencijalna povezanost HT i CC indukovanog HPV-om.

Ključne reči:
autoimunske bolesti; tireoiditis, limfomatozni; hepatitis, virus; papillomavirus, humani; rizik, procena; grlić materice, neoplazme.

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Introduction

Hashimoto's thyroiditis (HT) and cervical cancer (CC) induced by human papillomavirus (HPV) are distinct diseases; however, both are influenced by immune dysregulation and chronic inflammatory processes. Evidence suggests that viral agents, including Epstein-Barr virus (EBV), may contribute to autoimmune thyroid disorders by modulating immune responses (IRs), while HPV-driven carcinogenesis is strongly dependent on host immune surveillance and evasion mechanisms [1, 2]. Understanding the endocrine and immune mechanisms of HT and HPV infections is crucial for clarifying potential common pathogenic pathways [2, 3]. This knowledge may improve diagnostic and therapeutic approaches and enhance our understanding of the pathogenesis of both diseases [4]. In addition to HPV, EBV and hepatitis C virus (HCV) may also contribute to the development of autoimmune thyroid diseases (AITDs), indicating a broader spectrum of viruses involved [1, 5].

Immunopathogenesis of Hashimoto's thyroiditis

HT is an autoimmune disorder in which the immune system erroneously targets thyroid tissue, leading to progressive glandular damage and dysfunction [4, 6, 7]. The main pathogenic mechanisms include infiltration of T lymphocytes, cytokine-mediated immune activation, and the development of chronic inflammatory processes within the thyroid gland [4, 7]. In HT, the immune system produces autoantibodies, most commonly anti-thyroid peroxidase – anti-TPO and anti-thyroglobulin – anti-TG, which contribute to thyroid tissue destruction by targeting key proteins involved in thyroid hormone synthesis and storage [4, 7]. This persistent immune-mediated inflammation results in progressive impairment of thyroid function and reflects a state of immune dysregulation that may influence broader immune homeostasis [4, 7]. In addition, AITDs have been associated with infectious and environmental triggers that may contribute to immune system activation and dysregulation [6], highlighting the complex interplay between genetic susceptibility, IRs, and external factors in disease pathogenesis. Some studies suggest an association between HT and an increased risk of thyroid malignancies, particularly papillary thyroid carcinoma; however, evidence regarding associations with malignancies in other organs remains limited and inconclusive [8].

Human papillomavirus, immune response, and hormonal modulation in cervical cancer

HPV is the leading cause of CC, responsible for over 99% of cases, with HPV types 16 and 18 being particularly oncogenic [9]. HPV induces malignant transformation primarily by evading host immune surveillance, thereby reducing IR against infected cells. This immune evasion occurs due to HPV's ability to inhibit T lymphocyte and natural killer cell activity [2].

Hormonal factors, particularly estrogen and progesterone, play key roles in the progression of HPV infection. Estrogen enhances the expression of cellular factors that facilitate HPV entry, promoting infection [2, 9]. On the other hand, progesterone reduces T lymphocyte activity, leads to immune dysregulation, and weakens the IR to HPV [2, 10]. These hormonal influences, combined with HPV's immune evasion mechanisms, create a favorable environment for the development of cancer [11]. Additionally, hormonal fluctuations during the menstrual cycle can affect HPV persistence and IR, emphasizing the importance of hormonal regulation in CC development [2, 9, 12, 13].

Immune evasion mechanisms by viruses: Epstein-Barr, hepatitis C, and hepatitis D

Viruses such as EBV, HCV, and hepatitis D virus (HDV) contribute to immune evasion, reducing the immune system's ability to identify and eliminate infected cells. Chronic infections with these viruses can increase the risk of developing malignancies. For instance, EBV can establish latent infections and induce T cell exhaustion, contributing to immune dysregulation, promoting autoimmune diseases (ADs), including HT. Similarly, HCV and HDV induce chronic inflammation, impairing immune tolerance and the function of regulatory T cells, which are essential for preventing ADs. By leading to immune dysregulation, these viruses foster environments that increase the risk of both ADs and malignancies, including those linked to HPV infection [14–16].

Viruses and the development of Hashimoto's thyroiditis

Chronic viral infections, particularly EBV, play a significant role in the development of HT. Limited evidence suggests a possible association between EBV infection and AITDs, including HT, primarily through mechanisms of immune dysregulation and molecular mimicry. Similarly, HCV induces chronic inflammation that triggers auto IR, increasing susceptibility to HT, while HDV may also contribute to immune dysfunction and thyroid diseases [14–18].

Endocrine regulation, immune dysfunction, and hormonal influence

Thyroid hormones and sex hormones, particularly estrogen and progesterone, play an important role in modulating IRs. Estrogen has been shown to influence both innate and adaptive immunity, potentially enhancing susceptibility to persistent viral infections such as HPV, while progesterone may exert immunosuppressive effects on cellular IRs [19, 20].

In the context of HT, altered thyroid hormone levels may contribute to immune imbalance rather than generalized immunodeficiency. This endocrine–immune interaction may influence cytokine production and immune cell activity [21].

However, the extent to which the interplay between thyroid and sex hormones contributes to viral persistence and

malignancy risk remains insufficiently clarified, and current evidence is still limited [20, 21].

Common pathogenetic mechanisms and potential interactions between human papillomavirus, Hashimoto's thyroiditis, and other viruses

Although HT and HPV infection are distinct clinical entities, several overlapping mechanisms, involving immune dysregulation and chronic inflammation, may be implicated. In HT, the primary feature is not generalized immune suppression but rather dysregulation of immune tolerance, including altered regulatory T-cell function and persistent inflammatory response [22].

HPV, on the other hand, employs well-established immune evasion mechanisms that allow viral persistence and progression toward malignancy [23]. The coexistence of immune dysregulation in HT and viral immune evasion in HPV infection may theoretically contribute to prolonged infection and increased oncogenic potential; however, direct causal relationships have not been clearly established.

The role of additional viral infections, such as EBV and HCV, has been more extensively studied in the context of immune modulation and chronic inflammation [24]. In contrast, evidence regarding HDV remains limited and should be interpreted with caution.

Currently, there is a lack of robust epidemiological data directly linking HT with increased risk of CC. Therefore, proposed interactions between these conditions should be considered hypothesis-generating and require further investigation.

Conclusion

The endocrine-immune interactions between Hashimoto's thyroiditis and human papillomavirus infections, along with the involvement of viruses such as Epstein-Barr, hepatitis C, and hepatitis D, suggest common pathogenetic mechanisms that may increase the risk of malignancies. Reduced immune efficiency, hormonal fluctuations, and immune evasion strategies contribute to the development of both conditions. This understanding provides opportunities for improving diagnostic approaches and therapeutic strategies.

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