Parvovirus and Thyroid Cancer

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Parvoviruses are some of the smallest DNA viruses known to infect a wide range of animal species and humans. Though not all parvoviruses are pathogenic, some can cause disease ranging from asymptomatic to benign to life-threatening. Recently, there has been an interest in the possible role of parvoviruses in thyroid disease in general. The objectives of this review are to cite and appraise the available evidence on the role of parvoviruses in thyroid cancer in particular. Little to no evidence is available directly linking animal parvoviruses and thyroid cancer, but there is a growing literature on the human erythrovirus B19 (EVB19) and its association with thyroid cancer. Of particular interest is the persistence and expression of EVB19 DNA, RNA, and protein in a wide variety of thyroid tissues. While a causative role of EVB19 in the pathogenesis of thyroid cancer cannot be supported at this time, an indirect role is hypothesized and discussed but with the recognition that the data are limited. Further studies are clearly warranted to determine the exact, if any, role of this human pathogen in thyroid cancer.
Semin Oncol 42:304-308

Viruses have been implicated in thyroid diseases, particularly subacute thyroiditis and autoimmune thyroid diseases such as Hashimoto's thyroiditis and Graves' disease,[1] and also in thyroid cancer.[2] Among the viruses implicated are coxsackie virus,[3] Epstein-Barr virus (EBV),[4] erythrovirus 19 (EVB19),[5–7] hepatitis C virus,[8] herpes simplex virus (HSV),[9] human foamy virus (HFV),[10] human T-lymphotropic virus-1 (HTLV-1),[11] mumps virus,[12] and rubella.[13] Herpesviruses, including HSV-1/HSV-2,[14] and EBV,[15] simian virus 40 (SV40),[16] and EVB19 are among the implicated pathogens for human thyroid cancer. EVB19 and thyroid cancer will be the main focus of this review.

Thyroid cancers are the most common endocrine neoplasms. The most common type of thyroid cancer is papillary thyroid carcinoma (PTC), which is derived from thyroid follicular epithelial cells and considered well differentiated. Other less common types are follicular (FTC) and anaplastic (ATC), also derived from thyroid follicular epithelial cells. ATC is one of the most aggressive and deadliest of human cancers. Medullary thyroid carcinoma (MTC) is derived from parafollicular C cells. The incidence of thyroid cancer has been rising over the last three decades,[17] so a better understanding of the basic biology and possible contributing factors to pathogenesis is very important ultimately for patient care.

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Conflicts of interest: none
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0093-7754/ - see front matter

http://dx.doi.org/10.1053/j.seminoncol.2014.12.022

ANIMAL PARVOVIRUSES AND THYROID CANCER

Though there are no disease correlations, it is interesting that primary cultures of swine thyroid cells are frequently noted to be infected by porcine parvovirus upon isolation and passage.[18,19] In addition, there is an interesting report in the veterinary literature of a beaver that died of a "parvovirus-like" disease that also had a follicular thyroid carcinoma with pulmonary metastasis on necropsy.[20] The limitation of this association is that the infectious agent, if any, was not definitively identified, particularly in the thyroid tumor. The diagnosis was made solely on similarities of the clinical history and presentation (necrotizing ulcerative colitis) to parvoviral (canine or feline parvovirus) disease. However, this may have been the only observed correlation of a parvovirus and thyroid cancer in an animal, so it is worth mentioning.

The only other reported link between animal parvoviruses and thyroid cells are based on two reports by Vanacker et al.[21,22] In these studies, the minute virus of mice (MVMp; a murine parvovirus)

nonstructural protein (NS1) was shown to upregulate the thyroid hormone receptor alpha gene, and thyroid hormone T3 enhanced cytotoxicity by MVMp. Infection also led to changes in the ratio of THRalpha1 and 2, which is known to be inverted in transformed versus nontransformed cells. The overall data suggest that, at least for MVMp, under the described in vitro testing conditions in transformed rat fibroblast cell lines, animal parvoviruses are more likely to play a role in inflammatory thyroid disease, via thyroid cytotoxicity, and possibly play an antioncogenic role. The main caveat would be that the role may be different in thyroid cells than the tested fibroblast cells, and as we have found,[23] the human virus may lead to a different effect than the animal virus.

HUMAN ERYTHROVIRUS B19

EVB19, formerly parvovirus B19, is a small, nonenveloped single-stranded DNA virus[24] EVB19 belongs to the family Parvoviridae, genus Erythrovirus. The 5,596-nt genome encodes for one major non-structural (replication) protein (NS1) and two capsid proteins, VP1 and VP2. NS1 is known to induce apoptosis.[25] At least two other minor proteins are made but have not been completely characterized in terms of function.

EVB19 is an obligate human pathogen.[26] The only known permissive cells (allowing full viral replication) for EVB19 are erythroid precursor cells (burst-forming unit–erythroid [BFU-E] and colony-forming unit–erythroid [CFU-E]). However, EVB19 (at least the genomic DNA) is known to persist in a multitude of other cells.[27]

The majority of the adult population is seropositive for EVB19. Seroprevalence increases with age, though there is evidence of waning immunity after age 70 as well.[28] EVB19 is a cause of several human diseases from benign, such as erythema infectiosum (fifth disease), to life-threatening, including aplastic crisis and hydrops fetalis. It has been associated with a number of other human autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosis, and vasculitis.[5,26,29]

The association of EVB19 with human thyroid disease (Table 1) has been growing in the literature since 1994 when the first case report of EVB19 associated with subacute thyroiditis was reported.[30] In contrast to other thyroid disease associations made over the last two decades, EVB19 and thyroid cancer is a very young field. Though there are only three articles from two research groups in the literature that specifically link EVB19 to thyroid cancer (Table 2), a significant amount of work has been done in just over 5 years.

Since 2008, EVB19 has been associated with human thyroid cancers. Wang et al (2008) were the first to document in a relatively large Chinese cohort that EVB19 is present in papillary thyroid cancer, the most common form of thyroid cancer.[31] They documented not only the presence of the genome but also capsid protein. In their study, they did not find EVB19 associated with the less common forms of thyroid cancer, follicular (FTC) and medullary (MTC) thyroid carcinomas. This study did not assess the most deadly type of thyroid cancer, anaplastic thyroid carcinoma (ATC).

In 2011, our laboratory reported the association of EVB19 (presence of capsid protein) with PTC, but in contrast to Wang, also with other types of thyroid cancers, including ATC.[32] Differences in the findings from Wang et al[31] may have been due to geographic and genetic differences in the cohorts studied (Chinese v. Non-Chinese) or sampling differences given that only small numbers of samples of some forms of thyroid cancer can be obtained. In addition, technical differences could account for the variation in

Table 1. Primary Literature Specifically Linking EVB19 and Human Thyroid Disease

Publication Year	EVB19—Thyroid Disease Association	Type/Size of Study	Reference
1994	subacute thyroiditis	Case report	30
1998	subacute thyroiditis (negative study)	SAT cohort (N=9)	43
2007	Hashimoto's thyroiditis	Case report	7
2008	Hashimoto's thyroiditis	Age-matched controlled (N=73 HT; N=73 non-HT)	39
2010	Graves' disease	Prospective serum and tissue analysis (N=90)	37
2010	Hashimoto's thyroiditis	Retrospective FFPE tissue analysis (N=70)	38
2011	Hashimoto's thyroiditis	Retrospective FFPE tissue analysis (N=3)	32
2013	Graves' disease	Retrospective case-control (N=64)	36

Abbreviations: SAT, subacute thyroiditis; HT, Hashimoto's thyroiditis; FFPE, formalin-fixed paraffin-embedded.