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Review Articles

A review on uterine sarcomas and a brief report on the role of the notch pathway

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Summary

Background: Uterine sarcomas represent a rare type of tumor of the uterus (3-7%) with a poor prognosis. Many of the patients will be diagnosed at an advanced stage due to lack or insufficient symptoms. The majority of these tumors, despite common origin, will require a different approach for every patient and for every different form of cancer. *Objective:* To conduct a review of the literature providing an evidence-based summary of the available literature regarding uterine sarcomas, with a brief report to the Notch pathway that, according to the authors, should be further investigated as therapeutic anti-angiogenic factor. *Materials and Methods:* Medline was searched for uterine sarcoma related articles from about 1976 to 2015 including terms such as "uterine sarcoma", "leiomyosarcoma", "Müllerian tumors", and others. *Results:* Leiomyosarcomas (LMS) are considered the most common uterine sarcoma type and has a high risk of recurrence especially when diagnosed late. In addition to LMS, endometrial stromal sarcoma (ESS), arising from the connective tissues (stroma) of the endometrium, and adenosarcomas (mixed epithelial-nonepithelial neoplasms arising from endometrium) represent the major types of uterine sarcomas. Therapists will not easily suspect uterine sarcomas due to the absence of specific symptoms and diagnosis will be set only after hysterectomy. *Conclusion:* Since carcinosarcomas are more epithelial than stromal neoplasms, they are no longer categorized as uterine sarcomas. There are no sufficient symptoms for the disease. Surgery is the mainstay of therapy in early stages, while recent studies question the undefined role of adjuvant chemo/radiotherapy. The role of Notch pathway in uterine sarcoma needs to be further investigated for possible anti-angiogenic therapeutic role.

Key words: Adenosarcoma; Endometrial stromal sarcoma; Leiomyosarcoma; Müllerian tumors; Notch pathway; Uterine sarcoma.

Introduction

Uterine sarcomas represent a rare type of tumor of the uterus with a poor prognosis that depict a complex chapter for pathologists, since there are many debates concerning the pathogenesis, the diagnostic dilemmas, the classification of the disease, and the therapeutic options. Uterine sarcomas account for about 7% of new cases within the group of adult soft tissue sarcomas [1] and many of the patients will be diagnosed when tested for vaginal discharge, abdominal or pelvic pain, palpable mass, abdominal pressure, and other vague symptoms. The diagnosis will be made after hysterectomy and some of the patients will need adjuvant therapy that differs according to the sarcoma type. The prognosis will be affected by stage, type, grade, the patient's general health, and the therapy received.

Uterine sarcomas derive from mesenchymal cells, consisting of endometrial stroma, smooth muscle, and blood vessels, or admixtures of these, and they are divided into two basic groups, pure and mixed epithelial. These, in turn, are divided into subcategories of homologous (consisting of uterine tissue) – heterologous (consisting also of non-uterus tissue) tumors and further, depending on the tissue of origin [2, 3]: A) pure mesenchymal tumours - homologous: endometrial stromal and smooth muscle) and - heterologous (rhabdomyosarcoma and chondrosarcoma), B) Mixed epithelial mesenchymal tumours - mallignant mixed Müllerian (homologous and heterologous), and adenosarcoma

Until recent years, the most common types of all the uterine sarcomas were considered to be carcinosarcomas followed by leiomyosarcomas (LMS), endometrial stromal sarcomas (ESS), adenosarcomas, and undifferentiated uterine sarcomas [1, 3, 4]. Histologically, uterine carcinosarcomas were considered a type of uterine sarcomas and were classified as malignant mixed Müllerian tumors or mixed mesodermal sarcomas. Recent studies classify carcinosarcoma as a dedifferentiated/metaplastic form of endometrial carcinoma due to its deriving from neoplastic cells with characteristics of more epithelial than stromal neoplasm,

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Table 1. — *Comparison of the old and modern categorization of most common uterine sarcomas.*

Categorization before 2009		**Categorization after 2009**	
1	Carcinosarcomas (40 – 50%)	1	Leiomyosarcoma (60%)
2	Leiomyosarcoma (LMS) (30%)	2	Endometrial stromal sarcoma (15%)
3	Endometrial stromal sarcoma (15%)	3	Adenosarcoma and other uterine sarcoma (5-10%)
4	Adenosarcoma and other uterine sarcoma (5%)	4	Undifferentiated uterine sarcoma (5%)
5	Undifferentiated uterine sarcoma (5 %)	-	-

but also because of the epidemiology, risk factors, and clinical behavior associated more with endometrial carcinoma than sarcoma [4]. LMS is now regarded the most common uterine sarcoma with a percentage of 60%, although carcinosarcoma is still included in most retrospective studies of uterine sarcoma as in the 2003 World Health Organization classification [5] (Table 1).

LMS findings are usually mentioned with respect to their clinicopathological features. Nuclear atypia, high mitotic rate, extensive necrotic rate, hypercellularity, with one or more supportive clinicopathologic features, such as peri- or postmenopausal age, extrauterine extension, large size (over 10 cm), infiltrating border, necrosis, and atypical mitotic figures that are frequently present, lead to diagnosis although the final decision is made with precaution since some variant forms of LMS differ from the original findings (e.g atypical smooth muscle sarcoma) [6-8].

Endometrial stromal tumors are divided into endometrial stromal nodules (ESN), low grade endometrial stromal sarcomas, undifferentiated endometrial sarcomas (UES), and the recent 2014 WHO classification recognizes a subset as high grade ESS (a type associated with YWHAE-NUTM2 - an aggressive clinical behavior type with poor prognosis) [9, 10]. The main differentiation element for ESN from the common stromal sarcomas is the smooth, non-invasive margins [9]. In contrast, low grade ESS appears with infiltrative margins and distinctive growth as worm-like vessel invasion [11], while UES does not resemble endometrial stroma, displaying high grade atypia, pleomorphism, usually with high mitotic rate, and presence of necrotic tumor [12].

Histological analysis of adenosarcomas highlights the participation of a benign but sometimes atypical glandular component and a sarcomatous stromal component. In addition, even a low mitotic count, in case of periglandular cuffs concentrating the stroma around cystic glands, can set the diagnosis [8,13].

In all types of uterine sarcomas, the development of the disease seems to be common. There are plenty of symptoms recorded: vaginal discharge, meno-metrorrhagia, intermestrual bleeding, palpable pelvic mass, pelvic pain, frequent urination, sense of fullness in the pelvic area, and other types of unclear symptoms. Some people may remain asymptomatic. Many of these symptoms mentioned in the literature appear among the majority of the patients, identical with the common leiomyoma symptoms [3, 14, 15]: 1) abnormal vaginal bleeding, 2) palpable pelvic mass, 3) pelvic pain, and 4) uterine enlargement

Thus, although there is not a significant connection, several symptoms play a major role in the differential diagnosis.

Although the major risk factors are not still fully clarified, many causes are responsible for and associated with the disease.

Prior pelvic radiation and tamoxifen use are risk factors mentioned in many studies. In particular, tamoxifen, used for breast cancer, has been a controversial issue with regard to the risk of developing a malignant uterine sarcoma [8, 14, 16]. Gene mutations are also accounted as one risk factor in some studies. Mutation in RB gene (familial retinoblastoma) and TP53 tumor suppressor gene (Li-Fraumeni Syndrome) have shown increased risk of uterine sarcoma development [17].

There have also been studies reporting a racial distribution of the disease [18]. In 1985 Schwartz *et al.*, studied a group of 104 female patients, where a more frequent appearance of the disease in women of American-European origin was more evident than Asian-African [19]. Obesity, hypertension, and diabetes should also be mentioned due to their general connection to uterine cancer [20-23].

The average age of diagnosis in LMS is 51 years [24], while adenosarcoma is 58 years [25], and ESS affects younger women with the mean age being 42 to 58 years [26].

Since the mid-1980s, most studies supported an aggressive intervention in order to start immediate treatment while staging. The reason is the very high expansion rate of the disease even in clinical Stage I. Consequently, the diagnosis will be set after hysterectomy and only by the microscopic results since there are no unique macroscopic characteristics for these uterine tumors [3].

From the perspective of imaging, in both CT and MRI, the subtypes of uterine sarcomas have common imaging features and usually reveal large uterine masses with extensive hemorrhage and necrosis, an image not capable of setting a diagnosis. However, imaging of these tumors is crucial not only in staging but also for the management of the disease [27].

The International Federation of Gynecology and Obstetrics (FIGO) staging systems for vulva, cervix, endometrium, and sarcomas was revised in 2009. The FIGO staging aims at a better quality of cooperation between the

Table 2. — *The 2009 revised staging for uterine sarcomas by FIGO [5].*

A. LEIOMYOSARCOMA, ENDOMETRIAL STROMAL SARCOMA	
Stage 1 – Limited to uterus	
IA	Tumor limited to uterus < 5 cm
IB	Tumor limited to uterus > 5 cm
Stage II – Limited to true pelvis	
IIA	Tumor extends to the pelvis, adnexal involvement
IIB	Tumor extends to extra-uterine pelvic tissue
Stage III – Infiltrates into abdominal tissue	
IIIA	Tumor invades abdominal tissues, one site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV – Involves bladder / bowel mucosa or distant mets	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis
B. ADENOSARCOMA	
Stage I – Limited to Uterus	
IA	Tumor limited to endometrium/endocervix
IB	Invasion to < ½ myometrium
IC	Invasion to > ½ myometrium
Stage II – Limited to true pelvis	
IIA	Tumor extends to the pelvis, adnexal involvement
IIB	Tumor extends to extra-uterine pelvic tissue
Stage III – Infiltrates into abdominal tissue	
IIIA	Tumor invades abdominal tissues, one site
IIIB	More than one site
IIIC	Metastasis to pelvic and/or para-aortic lymph nodes
Stage IV – Involves bladder / bowel mucosa or distant mets	
IVA	Tumor invades bladder and/or rectum
IVB	Distant metastasis

therapists as well as a more reliable determination of the prognosis for the patients. Since uterine sarcomas were previously staged as endometrial cancers, without representing the actual clinical behavior, and since new imaging and surgical approaches have developed in the past decade, with more prognostic information available, a new corpus sarcoma staging system was developed based on the criteria used in other soft tissue sarcomas (Table 2).

Carcinosarcomas should be staged as carcinomas of the endometrium, while tumors of the uterine corpus and ovary/pelvis in association with ovarian/pelvic endometriosis should be classified as independent primary tumors [5].

Although uterine sarcomas have been studied for years, the prognostic factors still remain the most enigmatic parts considering the prognosis and the adjuvant therapy selected. The initial therapy for all uterine sarcomas consists of hysterectomy (and debulking of tumor if present outside the uterus), including peritoneal washings and sampling of suspicious nodules, with or without removal of the ovary and the fallopian tubes, depending on the stage of the disease and the individual therapist [28, 29]. Total abdominal hysterectomy with ovary preservation is considerable in early-stage premenopausal patients with LMS [30]. For ESS Stages I and II, total abdominal hysterectomy with bilateral salpingo-oophorectomy combined with pelvic and peri-aortic selective lymphadenectomy is recommended [31, 32]. Adenosarcomas without sarcomatous overgrowth (SO) do not require adjuvant therapy of any type [33]. Nevertheless, adenosarcomas with SO represent an aggressive form of the disease with a high recurrence rate with chemotherapy having therapeutic participation prospects [26, 34].

LMS are very aggressive with poor prognosis even when diagnosed at an early stage, having a 71% recurrence rate (15% to 25% with a median survival of only ten months) [35, 36]. Therefore, aggressive surgical cytoreduction at the time of initial diagnosis constitutes a main factor for good prognosis [37, 38] (Table 3).

There have been many reports regarding the connection between LMS to prognostic factors, giving promising information for both therapists and patients.Clinical stage at diagnosis has proven to be the only unquestionable prognostic factor. Stages I and II show a five-year-survival range from 39% to 65% while Stages III and IV mention a lower than 29% rate, sometimes even lower than 7% [30, 39, 40-42].

Age has also been evaluated as either an individual or a combined to stage prognostic stage factor for the LMS. Patients aged under 50-51 seem to have a better prognosis concerning recurrence and survival [29, 40].

Vascular space involvement is mentioned as an independent prognostic factor. Absence of vascular space is reported by some authors as a parameter for good prognosis in patients with LMS [40].

Many studies report a connection between mitotic count and prognosis supporting a significant impact on the latter. Some studies concluded that mitotic count with <10-15 mitotic figures / 10 high power fields reached up to 65%, while others mention the lack of it, acting as an independent prognostic parameter in patients with greater tumor stage [39, 40, 43, 44].

Pre- and perimenopausal women seem to have a statistically better prognosis than women of postmenopausal age [4,39]. Infiltrative tumor margins are connected to poorer prognosis [29, 39].

Although surgery alone is associated with a better prognosis than surgery combined with adjuvant chemotherapy and/or pelvic radiotherapy, there have been recent studies questioning this opinion, pointing out the still undefined role of adjuvant therapy [4, 28, 29, 39, 45, 46].

A graphical calculating system (nomogram) has also been created and approved for use by the American Cancer Society as both a diagnostic tool and as a predictor of response to therapy for LMS. This system includes parameters of age at diagnosis, tumor size, tumor grade, involvement of the cervix, locoregional metastases, distant metastases, and mitotic index after primary surgery [47].

Other parameters studied over time are tumor proteins

Table 3. — *Common therapeutic protocols for common uterine sarcoma types [38].*

LMS[1]	Stage I	Total abdominal hysterectomy + bilateral salpingo-oophorectomy	+ pelvic and periaortic selective lymphadenectomy ± CTX[4] – RT[5]
	Stage II		+ pelvic and periaortic selective lymphadenectomy ± CTX - RT
	Stage III		+ pelvic and periaortic selective lymphadenectomy ± lymph node dissection or sampling ± RT
	Stage IVa		± lymph node dissection or sampling + RT ± CTX
	Stage IVb		+ CTX ± Palliative RT
ESS[2]	Stage I	Exploratory laparotomy + total abdominal hysterectomy + bilateral salpingo-oophorectomy + omental biopsy + aspiration of abdominal fluid for cytologic evaluation	± CTX ± HT[6]- RT
	Stage II		± CTX ± HT- RT
	Stage III		+ pelvic and periaortic lymphadenectomy in clinically positive nodes ± CTX ± HT ± RT
	Stage IVa		+ pelvic and periaortic lymphadenectomy in clinically positive nodes ± CTX ± HT ± RT
	Stage IVb		+ pelvic and periaortic lymphadenectomy in clinically positive nodes ± CTX ± HT ± Palliative RT
UUS[3]	Stage I	Total abdominal	± CTX - RT
	Stage II	Hysterectomy+ bilateral	± CTX - RT
	Stage III	Salpingo-oophorectomy	+ pelvic and periaortic lymphadenectomy in clinically positive nodes ± CTX
	Stage IV		+ pelvic and periaortic lymphadenectomy in clinically positive nodes ± CTX

[1] LMS: leiomyosarcomas, [2] ESS: endometrial stromal sarcomas, [3] UUS: undifferentiated uterine sarcomas, [4] CTX: chemotherapy, [5] RT: radiotherapy, [6] HT: hormonal therapy.

(p53, p16), antigens (Ki-67), and genes (Bcl2 family proteins) that leave possibilities of identifying types of LMS with a favorable prognosis based on staining with a panel of immunomarkers for cell proliferation and apoptosis. Yet, further studies are required to reach safer conclusions [30, 36, 39, 43, 48].

Studies on prognosis have been conducted for other main types of uterine sarcomas. LMS is the most studied form of uterine sarcomas and this definitely gives a better precedence, if not for treatment and prognosis, but definitely for general knowledge and guiding patients.

ESS is also a type of uterine sarcoma with grade and stage being the main prognostic factor. Early tumor stage and low myometrial invasion is connected to better prognosis [42, 49, 50]. Low-grade ESS has a five-year-survival rate of 90-100%, while high-grade ESS is an aggressive neoplasm with 55% five-year-survival. The mitotic index and the tumor cell necrosis is also reported as notable coefficient for prognosis [11, 43, 50]. In addition, nuclear atypia and necrosis, when used under strict criteria for 2003 WHO diagnosis, give a stronger and more reliable prognosis [51]. Expression of estrogen and/or progesterone, as well as nodal metastasis, are reported to be considerable prognostic factors while bilateral salpingo-oophorectomy as primary treatment and cytoreductive resection of recurrent lesions should be considered for improving survival [52, 53]. Adjuvant radiotherapy is an independent prognostic factor that some authors correlate to a better prognosis even in low grade ESS [54]. In general, ESS has much better prognosis than LMS. Post-relapsed survival of patients with low grade ESS can be expected to be more than a decade when treated with surgery and hormonal therapy [11, 43].

Most of the patients with early stage adenosarcoma have a favorable prognosis. Existence of sarcomatous overgrowth, age, stage, lymphovascular invasion, and tumor cell necrosis are prognostic factors studied and connected to the progression of uterine adenosarcoma, a disease with favorable prognosis in general [25, 42, 43, 55-57] and with a five-year-survival of 79% for Stage I, and 48% for Stage III. These rates become crucially affected by tumor invasion to the uterus wall and spread beyond the uterus limits [56].

Since LMS has aggressive behavior and is rarely cured when it recurs with metastatic disease, recurrence rates are expected to be high. The patients face a probability of recurrence of 53% up to 71% with the main sites being pelvic (0-17%), extrapelvic (8-29%), lung (54-37%), and other (15-4%), rates varying when radiotherapy is added to the initial treatment [35, 58].

The recurrence for ESS patients ranges from 30-50% with the main site being pelvis and lower genital tracts [26, 59]. Low grade ESS has good prognosis (even the high recurrence rates after the initial treatment), with lower rates in patients with non-ovarian preservation therapies (66.7% *vs.* 37.5%). Hormonal therapy, radiotherapy, and surgical excision of the metastasis are recommended for recurrences [26]. Post-relapse survival of patients with ESS can be expected to be >10 years, when treated with repeated surgical resection and hormonal therapy or both [60, 61]. Especially for low-grade ESS, hormonal therapy with medroxyprogesterone, tamoxifen, gonadotropin releasing hormone (GnRH), analogues, and aromatase inhibitors are suggested for Stages III-IV and for recurrent disease [32].

With the exception regarding the presence of sarcomatous overgrowth or invasion of the myometrium, adenosarcomas present weaker potential malignancy, late-

onset postoperative recurrence (25%), rare metastasis, and a higher incidence in older women [62]. In both local and distant adenosarcoma recurrence, the metastatic tissue most of the time consists of pure sarcoma, appearing mostly in the vagina, pelvis, or abdomen and as mentioned, long-term follow up is vital since recurrence may occur in a distant postoperative time [8].

Angiogenesis (de novo vessel creation), vasculogenesis (the differentiation of precursor cells into endothelial cells forming a primitive vascular network respectively), and vascular maintenance are all essential for tumor growth and metastasis. Chemical signals trigger the rapid creation of new vessels that support tumor growth. While various mechanisms are proven to participate on this procedure, detecting the receptors and inhibitors of these processes have provided much important information on both understanding tumor development but also on treating different malignancies [63, 64].

Vascular endothelial growth factor (VEGF) is an important regulator of vessel creation. Through the VEGF pathway, angiogenesis is activated only when VEGF binds to receptors on endothelial cells. Activation of the VEGF-receptor (VEGFR) triggers a cataract of signaling processes that stimulates endothelial cell growth, migration,. and survival from pre-existing vasculature. Three types of VEGF receptors are identified in mammals: VEGFR-1 and VEGFR-2, which are located on the endothelial cells of blood vessels and VEGFR-3 that is located on the endothelial cells of lymphatic vessels [65].

The cascade of events that leads to angiogenesis starts when tumor cells release VEGF (ligand protein) that reacts with the VEGFR (receptor) of endothelial cells of nearby vessels. A number of VEGF are identified that bind and activate the receptors on the nearby vessels. VEGF-A, VEGF-B, and placental growth factor (PlGF) interact with VEGFR-1. VEGF-A, VEGF-C, and VEGF-D bind to and activate VEGFR-2. VEGFR-1, and VEGFR-2 promote angiogenesis. On the contrary, VEGFR-3 interacts with VEGF-C and VEGF-D, stimulating lymphangiogenesis. When VEGF binds to two receptors, it activates transphosphorylation of the intracellular domains of the receptors and angiogenesis is initiated. Tumors have been proved to express several different VEGF ligands simultaneously, however, VEGFR-2 is considered to be the main receptor in the process of angiogenesis [65, 66].

To date, the anti-angiogenic therapies for tumor growth aim at blocking the VEGF pathway and in combination with chemotherapy, very promising results can be achieved [67]. When the crucial role of angiogenesis during tumor growth was identified, therapies aimed at creating factors blocking the responsible pathways, and until recently, blocking VEGF and VEGF receptors were considered to be the best validated approach. However, clinical and experimental studies targeting the VEGF pathway, often ineffective, proved that VEGF has an important but not a major role in tumor angiogenesis. Nowadays, it is widely accepted that other pathways have central role in vascular function and tumor angiogenesis. The Notch signaling pathway, a type of cell-to-cell signaling, is proved to play a key role in tumor angiogenesis and especially Delta like ligand 4 (Dll4), one particular ligand of the Notch receptor [64, 67-71].

When the Notch pathway is triggered, a sequence of proteolytic cleavages of the receptors is initiated; ligand proteins bind to the extracellular domain. Thus, cleavage and release of the intracellular domain is induced, which enters the cell nucleus to modify gene expression. Each of the cells follows a diverted biochemical way [72].

The Notch signaling pathway mediates, as mentioned, cell fate destinations and it is a vital parameter for every local cell-to-cell communication system. It coordinates a signaling pathway which involves gene regulation mechanisms that control multiple cell differentiation procedures. It is involved in various processes during embryogenesis, organogenesis, and self-renewal of cells and tissues [73, 74].

The Notch cellular receptors (NECD-NTMIC) are single pass transmembrane receptor proteins that consist of an extracellular (NECD), a transmembrane (TM), and an intracellular domain (NICD), normally triggered via direct cell-to-cell contact. There are four receptors identified in mammals (NOTCH 1, NOTCH 2, NOTCH 3, and NOTCH 4). These receptors are processed in the endoplasmic reticulum and Golgi within the signal-receiving cell. Cleavage and glycosylation generate calcium-stabilized hetero-dimer of NECD, non-covalently attached to the TM-NICD, that is inserted in the membrane. According to one model, with the converting enzyme TACE (ADAM-17) the NECD is cleaved away from TM-NICD and the processed NECD is endosome-transported (endocytosis) through the signal-send cell plasma membrane. As a result, the NECD part is recycled in the signal-sending cell plasma while γ-secretase releases NICD from TM in the signal-receiving cell. The NICD part enters nucleus and with the activation of CSL transcription factor complex (P300/MAML/ NICD/CSL), allows nuclear translocation resulting in activation of the canonical notch target genes. Notch agonists include Jagged (Jag1–Jag2) and Delta-like ligand (DLL1, DLL3, and DLL4) proteins [75, 76] (Figure 1).

Delta-like proteins are Drosophila protein Delta mammalian homologs that participate as ligands for the Notch 1, 3, and 4 pathway receptors. In humans, Dll4 is encoded by Dll4 gene and although most Notch receptors and ligands are expressed in many cell types, Dll4 reveals a highly selective expression pattern within the vascular endothelium, and especially in mature arteries and in actively growing vessels. Thus, it is considered to have a crucial role on promoting angiogenesis via the Notch system [77].

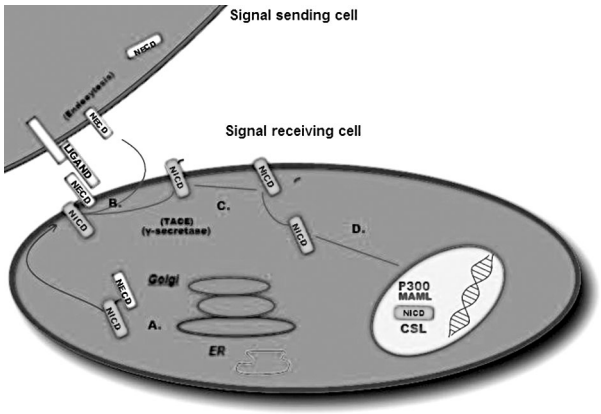

Figure 1. — The notch pathway. A) Construction of the receptor in the endoplasmic reticulum and Golgi. B) With the converting enzyme TACE the NECD is cleaved away from TM-NICD and the processed NECD is endosome-transported through the signal-send cell plasma membrane. Then, the NECD part is recycled in the signal-sending cell plasma. C) γ-secretase releases NICD from TM in the signal-receiving cell. D) The NICD part enters nucleus and with the activation of CSL transcription factor complex (P300/MAML/NICD/CSL) and allows nuclear translocation resulting in activation of the canonical notch target genes.

As previously mentioned, uterine sarcomas account for about 7% of new cases within the group of adult soft tissue sarcomas. Despite the fact that there are not enough studies conducted for both uterine sarcomas and anti-angiogenic factors (due to the rarity of these tumors and newly established therapies respectively), many theories have to be examined to reach safe conclusions and develop a better approach on both the disease and modern therapies as well.

Since angiogenesis is of vital importance for tumor growth (including soft tissue sarcomas) [71, 78-81], subsequently, the Notch pathway and Dll4 proteins could be crucial for angiogenesis in uterine sarcomas too.

The angiogenic profile of soft tissue sarcomas was examined in 2006 by Yoon *et al.*, when a panel of circulating angiogenic factors and a pattern of 200 angiogenesis-related genes were analyzed on the plasma of 108 patients with primary soft tissue sarcoma. The authors reported that Notch 1 and 4 were among the most highly up-regulated genes between soft tissue sarcomas (although the study didnot aim at measuring the expression of Dll4) [80].

In 2012 Rota *et al.*, published a study in BMC medicine, where the authors reviewed the role of the Notch signaling pathway in pediatrics soft tissue sarcomas and the use of modern notch signal inhibitors. Ewing sarcoma, synovial sarcoma, and rhabdomyosarcoma were the sarcomas analyzed in this study. The authors reported a significant role of all the notch receptors (especially Notch 1 and 3) not only on apoptosis, growth, migration, and invasion of tumor cells, but they also concluded that the inhibition of Notch pathway might be a promising approach on treating (pediatric) soft tissue sarcomas [81].

Several recent publications demonstrated that blockage of Notch-Dll4 results in tumor growth inhibition due to inefficient angiogenesis, promoting the idea of Dll4 being considered as a potential treatment for uterine sarcoma.

Rigdway *et al.*, reported in 2006 that Dll-4 is exclusively linked to angiogenesis –since neutralizing Dll-4 had no effect on intestinal goblet cell differentiation- with a less important role on vessel maintenance. Thus, blocking Dll-4 results in a well-tolerated and effective inhibition of tumor growth. In addition, Noguera-Troise *et al.*, as well as Thurston *et al.*, both in 2007 confirmed the previous statement. In their studies, inhibition of Dll-4 reduced tumor growth although a paradoxical vascularity was promoted, which, however, was non-productive [81-83].

In 2009, Hoey *et al.*, published in Cell Stem Cell Journal a study where the authors created anti-human and anti-mouse Dll4 antibodies to analyze the results of selectively targeting Dll4 in the tumor, vasculature, and stroma of the primary human tumor xenograft. The authors reported that inhibition of Dll4 signaling in human tumor cells with 21M18 antibody (anti-Dll4), selectively binding to human Dll4, decreased tumor growth in colon and breast tumors and caused a delay in tumor recurrence (when initially treated with chemotherapy), and a reduction in the percentage of tumorigenic cancer stem cells (CSC) [69]. Identically, Fisher's *et al.*, also studied in 2010 the anti-Dll4 therapy. Cetuximab - an EGFR therapeutic antibody- was effective only against wild type but not against mutant KRAS colorectal xenograft tumors, where anti-Dll4 factor did not only decrease both wild-type and mutant KRAS colon tumors (either single or combined to irinocetan), but also promoted apoptosis in tumor cells [84].

In the same year, Roma *et al.*, also stated that inhibition (both pharmacological or genetical blockage) of Notch pathway leads to reduction of rhabdomyosarcoma invasion cell lines. Through a real time PCR, the authors calculated pathway components for RMS and cell lines. The Notch pathway was widely expressed in RMS while its inhibition decreased morbidity and invasiveness of RMS cells.The authors suggested that blockage of Notch mechanisms should be considered as a potential therapy for metastatic rhabdomyosarcoma [85]. Additionally, in 2011 Gurvey and Hoey reported in Vascular Cell Journal that the anti-Dll4 factor was proved to attack cancers with two mechanisms. It was both the anti-angiogenic and anti-CSC activities, especially when combined to chemotherapy, that contributed to an overall anti-tumor efficacy and even the upregulation of VEGF when Dll4 is inhibited, is led however to immature non-functional vessels, supporting the idea of using anti-Dll4 antibodies for cancer therapy [70].

Discussion

The studies conducted so far lack on data considering the angiogenic profile of these tumors, although such therapeutic approach has proven to be essential for other type of malignancies. Therefore, it is very important to further investigate therapeutic anti-angiogenic drugs for uterine sarcomas too. The Notch signaling pathway seems to have a crucial role in the development of soft tissue sarcomas, and since Dll4 has a major role on the Notch system's angiogenesis, inhibition of Dll4, and Notch pathway should be considered and consequently tested as a potential therapeutic use for uterine sarcomas too, although additional research is needed to confirm such a claim.

Conclusion

Uterine sarcomas represent a rare disease of the uterus that requires immediate confrontation and therapeutic guidance. Since diagnosing the malignancy, each patient will have to face the difficult and stressful procedure of staging, followed by a selection of the appropriate therapy. Age, fertility, overall state of health, personal considerations, and the risk of each potential therapy are only a few of the factors that both the therapist and the patient will have to take into consideration in order to choose the appropriate treatment. While there is a great progress on both diagnosis and treatment, with a constant international literature update, the major issue the patient will have to deal with is still the option of treatment. The role of radiation and hormonal therapy are still not clearly specified creating doubts on the efficacy of the selected therapy. The effort of generating new methods on identification and prognosis of uterine sarcomas creates a feeling of safeness, predisposing a promising therapeutic future, but at the same time, promote the need for further research. It is commonly accepted that such malignancies need essential approach with new therapies being the center of attention in order to achieve a better prognosis for the patients

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