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Original Article

Evidence for a Novel Endometrioid Carcinogenic Sequence in the Fallopian Tube With Unique Beta-Catenin Expression

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Summary: Epithelial proliferations in the fallopian tube have been characterized by some as stem cell outgrowths (SCOUTs) and divided into type I and type II. Type II SCOUTs exhibit diffuse cellular beta-catenin nuclear staining (β-catenin$^+$), implying a *CTNNB1* mutation. SCOUTs are more common in perimenopausal and postmenopausal women and are associated with ovarian cancer but have not been linked directly to malignancy. We analyzed type II SCOUTs in various gynecologic conditions, and searched for endometrioid atypical hyperplasias (tubal endometrioid intraepithelial neoplasia) or adenocarcinomas in the tube. β-catenin$^+$ SCOUT frequency in cases of neoplasia was 66.7% per case and 30.7% per nonfimbrial cross-section for uterine endometrioid carcinomas versus 25% and 13.3% for controls, respectively ($P = 0.02$ and 0.09). Multiple (3 or more) β-catenin$^+$ SCOUTs in a single section were uncommon; 6 of 9 were associated with a carcinoma or proliferative lesion in the endometrium. Tubal endometrioid intraepithelial neoplasia/atypical hyperplasia displayed complex growth, including focal cribriform growth patterns and squamous morules. Two cases of type II SCOUTs associated with tubal endometrioid intraepithelial neoplasia/atypical hyperplasia and/or adenocarcinomas in the fallopian tube were identified, both of which coexisted with a separate endometrioid adenocarcinoma, one with bilateral ovarian endometrioid adenocarcinomas. Both benign and neoplastic tubal lesions were β-catenin$^+$. This report is the first to link components of a unique β-catenin$^+$ endometrioid carcinogenic sequence in the fallopian tube. It further emphasizes the multifocal nature of endometrioid neoplasia in the female genital tract and poses questions regarding the frequency and biologic underpinnings of β-catenin$^+$ proliferations in the oviduct. **Key Words:** Fallopian tube—Endometrioid—Adenocarcinoma—SCOUT—Beta-catenin.

The fallopian tube has emerged as a credible site for many pelvic epithelial malignancies, most notably high-grade serous carcinomas (HGSC). The serous carcinogenic sequence has been described in some detail, including early serous proliferations (p53 signatures and serous tubal intraepithelial lesions) and serous tubal intraepithelial

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carcinomas (STICs) either of which might contribute to an eventual HGSC (1–5). The latter are encountered in ~5% of fallopian tubes of asymptomatic women with germline *BRCA1* or *BRCA2* mutations and from 10% to 61% of women with symptomatic HGSC (6,7). The entire carcinogenic sequence is noted for a deleterious mutation in *TP53* and specific mutations are shared by both precursors and metastatic carcinomas (4,8).

Other epithelial proliferations have been described in the fallopian tubes, either incidentally or from women with borderline or malignant epithelial tumors, most recently given the term secretory (or stem) cell outgrowths (SCOUTs) (9). These proliferations do not appear to harbor mutations in *TP53*. They are found in the proximal as well as the distal fallopian tube, more common with increasing age and are more commonly discovered in women with extrauterine HGSC, albeit with no clear link to the associated neoplasms (10). They have been subdivided into 2 categories including so-called type I secretory cell outgrowths, which closely recapitulate normal tubal differentiation with cilia, and type II secretory cell outgrowths, which closely mimic endometrioid differentiation. Both are devoid of PAX2 expression with type I lesions lack expression of PAX2 and the biomarker alcohol dehydrogenase 1 ALDH1-similar to STICS-and show normal beta-catenin (membranous) localization. In contrast, type II SCOUTs exhibit strong ALDH1 and beta-catenin nuclear and/or cytoplasmic (β-catenin$^+$) staining (11,12).

Direct links between SCOUTs and neoplasia are limited. Multiple type I SCOUTs-specifically papillary lesions-have been occasionally associated with low-grade serous neoplasia (13,14). In contrast, excepting occasional proliferative lesions or those with squamous morules, type II SCOUTs have not been linked directly to malignancies in the fallopian tube. However, *CTNNB1* mutations have been associated with approximately one half and one quarter of endometrioid adenocarcinomas of the uterus and ovary, respectively, and confer a greater risk of adverse outcome (15–17). β-catenin$^+$ immunostaining carries a high specificity for *CTNNB1* mutations but is rarely diffuse in its distribution (18–20). Recently, we discovered 2 cases of endometrioid adenocarcinoma in the fallopian tubes that exhibited β-catenin$^+$ that was shared with type II SCOUTs, suggesting an endometrioid carcinogenic sequence initiating as in these otherwise benign-appearing lesions. We also cataloged the frequency of type II SCOUTs in the fallopian tubes of women with epithelial neoplasia in the reproductive tract and describe proliferative lesions that may signify tubal endometrioid intraepithelial neoplasms.

METHODS

This study was approved by the Institutional Review Board at Brigham and Women's Hospital.

Identification of Potential Cases

Since 2005, the Women's and Perinatal Division at Brigham and Women's Hospital has employed the SEE-FIM protocol for examining the distal fallopian tube in all cases of uterine or ovarian epithelial neoplasia. This protocol has been the basis for the discovery of epithelial proliferations of the fallopian tube with attention to secretory cell outgrowths since 2010 (9). Under this protocol, examination of each tube is performed with attention to the presence of either secretory cell outgrowths, serous tubal intraepithelial proliferations or lesions of undetermined significance, and STIC (2,4,5). Cases selected for review fell under this protocol.

Recognition of Type II SCOUTs

Type II SCOUTs were identified by the following: (1) a discrete process that could be distinguished on hematoxylin and eosin staining from the surrounding salpingeal epithelium, (2) manifesting as a pseudostratified epithelium with (3) inconspicuous cilia and slightly larger and taller elongated nuclei, presenting with an "endometrioid" appearance (Figs. 1A, B, Supplemental Figs. 1A–D, Supplemental Digital Content 1, http://links.lww.com/IJGP/A89). Type II SCOUTs were usually distinguishable from so-called "p53 signatures" (Supplemental Fig. 1E, Supplemental Digital Content 1, http://links.lww.com/IJGP/A89) by a taller cell population but not invariably from other proliferations (Supplemental Fig. 1F, Supplemental Digital Content 1, http://links.lww.com/IJGP/A89); therefore β-catenin staining was the benchmark for confirming their presence.

Characterization of β-catenin$^+$ Type II SCOUTs

Cases of endometrial and ovarian endometrioid neoplasia, ovarian mucinous neoplasia, extrauterine serous carcinoma and controls were identified, and blocks corresponding to fallopian tube epithelium were retrieved from archives and sectioned. In all cases the entire distal fallopian tube was submitted for evaluation and the assessment of β-catenin$^+$ SCOUTs was made by one of us (C.P.C.) by immunohistochemical review to avoid misclassification by hematoxylin and eosin staining alone. Sections were stained for β-catenin (cat # 810154; BD Biosciences, San Jose, CA) using the Envision system and antibody diluted at 1:1000. Epithelium with nuclear and/or cytoplasmic staining was scored as β-catenin$^+$ (Fig. 1B,

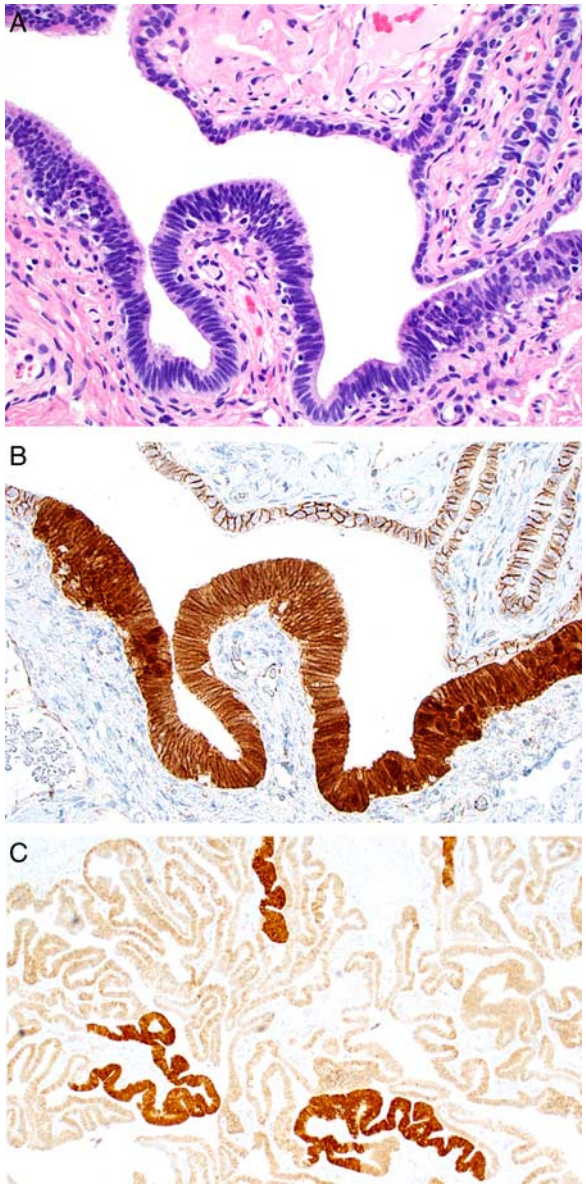

FIG. 1. (A) Hematoxylin and eosin–stained section of a type II stem cell outgrowths (SCOUT) showing a pseudostratified epithelium similar to endometrial epithelium. (B) Beta-catenin staining highlights both nucleus and cytoplasm. (C) Multiple type II SCOUTs in a cross-section of fallopian tube of a woman with a coexisting endometrioid adenocarcinoma.

Supplemental Fig. 2, Supplemental Digital Content 1, http://links.lww.com/IJGP/A89). The number of β-catenin$^+$ type II SCOUTs was tabulated as was the number of cross sections or section fragments (in the case of fimbria) in a slide. The maximum number of β-catenin$^+$ SCOUTs seen in a single cross section was also computed. Overall frequency was expressed as average number of β-catenin$^+$ SCOUTs per cross section. Cases in which abundant-at least 3 in 1 cross-section β-catenin$^+$ SCOUTs were noted. Controls consisted of women undergoing routine hysterectomy and salpingectomy for nonmalignant conditions.

Type II β-catenin$^+$ SCOUTs With Epithelial Atypia

Consult files were reviewed for endometrioid proliferations in the tube including the descriptors "endometrioid hyperplasia," "benign epithelial hyperplasia," or "epithelial hyperplasia," and "squamous morular metaplasia" (or squamous morules). These cases were immunostained for β-catenin where possible and their histopathology characterized.

Type II SCOUTs and Tubal Endometrioid Adenocarcinoma

The presence of β-catenin$^+$ tubal endometrioid carcinomas was determined from review of all cases of tubal endometrioid carcinoma received between 2005 and 2018, including cases associated with coexisting endometrial or ovarian endometrioid adenocarcinoma. Where available, fallopian tubes were reviewed to determine if type II SCOUTs were present and/or associated with β-catenin$^+$ staining. Furthermore, attention was paid to the presence of features suggesting endometrioid neoplasia. These included (1) squamous morules, (2) clusters of crowded gland-like β-catenin$^+$ epithelium, and (3) glandular atypia. When abnormalities in epithelial architecture with crowding or atypia were identified the lesions were arbitrarily termed tubal endometrioid intraepithelial neoplasia or TEIN/atypical hyperplasia. This was not to equate these proliferations with conventional endometrial EIN/atypical hyperplasia but to separate them from type II SCOUTs without epithelial complexity.

TABLE 1. *Frequency of β-catenin^{N+} type II stem cell outgrowths in normal tubes of cases and controls as a function of case number and histologic section number*

	Cases	Positive	%	*P*	Sections	Positive	%	*P*
Controls	12	3	25		30	4	13.3	
EMCA ovary	7	2	28.6	1	35	2	5.7	0.40
Mucinous neoplasia ovary	33	8	24.2	1	121	8	6.6	0.26
EMCA uterus	35	24	66.7	0.02	78	24	30.7	0.09
HGSC	13	7	53.8	0.23	31	7	22.5	0.41

EMCA indicates endometrioid adenocarcinoma; HGSC, extrauterine high-grade serous carcinoma.

TABLE 2. *Breakdown of cases with multiple type II SCOUTs, TEIN, and associated β-catenin^{N+} adenocarcinoma*

Category	Case	Age (yr)	Coexisting Pathology
3 or more type II SCOUTs in 1 cross-section	1	49	EMOID carcinoma uterus
	2	47	HGSC
	3	46	LGSC
	4	73	EMOID carcinoma uterus
	5	58	EIN with Morules extraovarian serous borderline tumor
	6	44	EMP with gland crowding
	7	45	Adenomyosis
	8	44	EMOID carcinoma uterus and ovaries STIC in one fallopian tube
	9	71	EMOID carcinoma uterus
Type II SCOUT with associated TEIN	10	62	Left ovarian cyst
	11	52	EMOID carcinoma uterus, metastatic
	12	44	EMP
	13	83	History of colon cancer
Type II SCOUT with tubal EMOID adenocarcinoma	14	44	See case 8
	15	71	See case 9

EIN indicates endometrial intraepithelial neoplasia; EMOID, endometrioid; EMP, endometrial polyp; HGSC, extrauterine high-grade serous carcinoma; SCOUT, stem cell outgrowth; STIC, serous tubal intraepithelial carcinoma; TEIN, tubal endometrioid intraepithelial neoplasia.

RESULTS

Frequency of β-catenin$^+$ Type II SCOUTs

Table 1 summarizes the frequency of β-catenin$^+$ type II SCOUTs in the fallopian tubes of controls and various endometrioid or serous tumors. In general, β-catenin$^+$ SCOUTs displayed diffuse staining throughout the cell, with less conspicuous membrane staining. Nuclear staining was either inconspicuous or focal (Supplemental Figs. 2C–F, Supplemental Digital Content 1, http://links.lww.com/IJGP/A89). Staining was computed both as number of cases with at least one type II SCOUTs and as number of cross-sections containing a type II SCOUTs. With respect to number of cases with a type II SCOUT, there were no significant associations relative to controls except for endometrioid endometrial carcinomas ($P = 0.02$). The mean ages of 43 cases with (53.1 yr) and 45 without (55.4 yr) type II SCOUTs in the entire group were not significantly different. This contrasts with a prior study by Quick et al. (10) noting a significant association between mean age and PAX2-SCOUTs frequency; however, in that study comparisons were made with fallopian tubes obtained from pediatric and postpartum controls, both of which rarely displayed SCOUTs of any type. Cases with 3 or greater SCOUTs in 1 or more cross-section were uncommon (Table 2). Of 9 cases, 6 were under age 50 (Table 1, cases 1–9) and several were associated with endometrioid lesions of the uterus.

Type II β-catenin$^+$ SCOUTs With TEIN/Atypical Hyperplasia

Five cases were identified and reviewed and their association with neoplasia is summarized in Table 2 (cases 10–13 and 8). The degree of gland complexity associated with lesions designated as TEIN varied. Some foci contained gland crowding with (Fig. 2A) or without (Fig. 3A) squamous morules. Others displayed papillary growth or isolated endometrioid glands with intraglandular cribriform growth (Fig. 2B). In one case, extensive linear superficial epithelial growth was punctuated by small microglandular or squamoid patterns (Fig. 2C). All but one case tested was β-catenin$^+$ (Figs. 2D, 3B).

Type II β-catenin$^+$ SCOUTs and Coexisting β-catenin$^+$ Tubal Endometrioid Adenocarcinoma

Two cases of β-catenin$^+$ endometrioid adenocarcinomas of the fallopian tube were discovered on routine pathology review, either because of the presence of a type II SCOUT [case 14 (8)] and/or multiple SCOUTs and an TEIN [case 15 (9)].

Case 8 displayed both a primary uterine FIGO grade I–II endometrioid and bilateral ovarian endometrioid adenocarcinomas. All 4 tumors were immunostained and diffuse β-catenin$^+$ was limited to the tubal carcinoma. In the remaining tumors β-catenin staining was either exclusively or largely cytoplasmic. Two additional findings in the fallopian tube were multiple type II SCOUTs and foci of TEIN, all exhibiting diffuse β-catenin$^+$ (Figs. 3A–C) and a single focus of STIC (not shown) that exhibited normal staining for β-catenin but showed strong nuclear p53 immunostaining and an elevated proliferative (Ki-67) index.

Case 9 displayed FIGO grade I endometrioid adenocarcinomas of the endometrium and fallopian tube, the latter in association with a type II SCOUT.

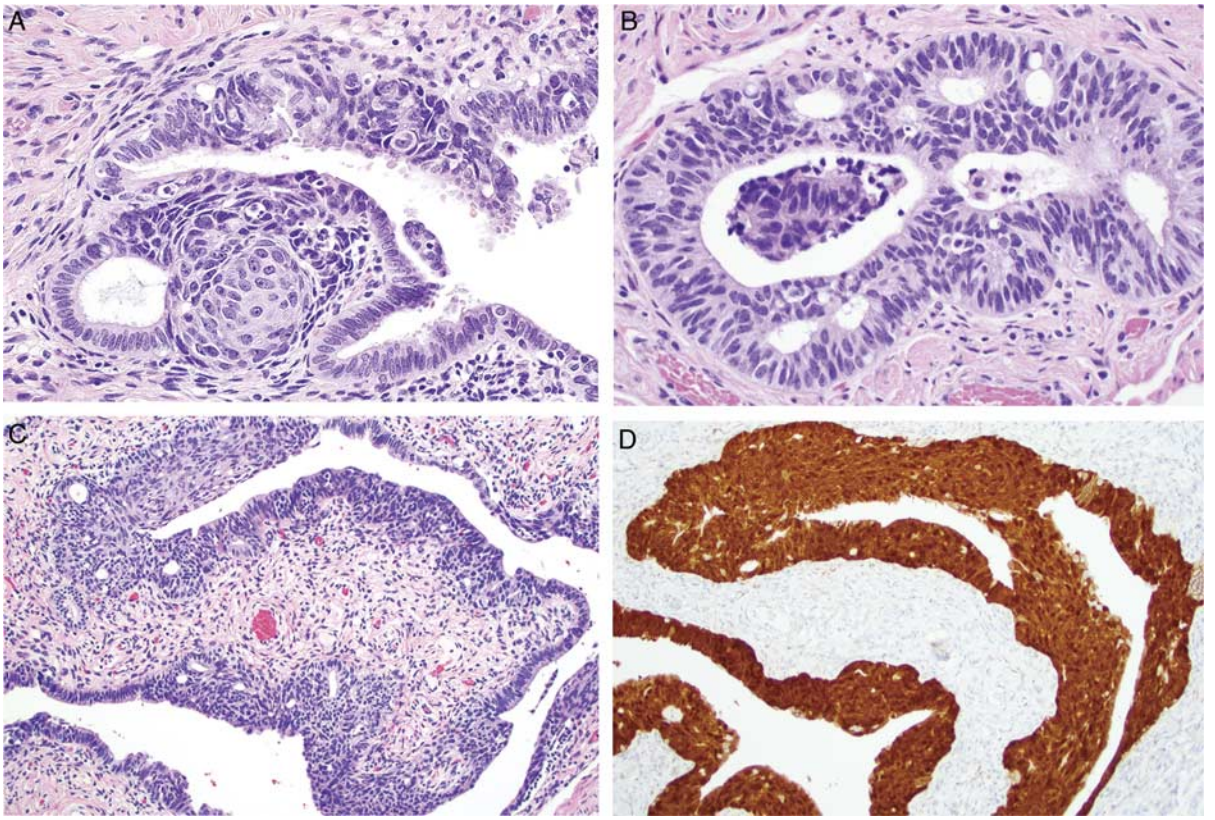

FIG. 2. (A–C) Proliferative type II stem cell outgrowths or tubal endometrioid intraepithelial neoplasia, displaying morules (A), focal cribriform architecture (B) or a blend of epithelial stratification and squamous differentiation (C); (D) corresponding beta-catenin staining for case in (C).

Both SCOUT and adenocarcinoma were β-catenin$^+$ in contrast to the endometrial primary.

In summary the above 2 cases displayed concurrent endometrioid adenocarcinomas of the uterus-with or without an associated ovarian tumor-and fallopian tube. Strong β-catenin$^+$ characterized the fallopian tube tumors and TEINs when present.

DISCUSSION

The fallopian tube is best known for the presence of precursors to HGSC, which contain mutations in *TP53* and include early serous proliferations (i.e. p53 signatures and serous tubal intraepithelial lesions) and STICs (2,4,5). Although attention has focused on this carcinogenic sequence, other epithelial proliferations have been described in the tube (14,21–23). Many of those described were papillary proliferations, some associated with serous borderline tumors. We described 2 types of proliferations or so-called SCOUTs, including those with papillary architecture and prominent cilia similar to the former (type I SCOUTs) and those described in this report (type II) (10–13). Although a uniform nomenclature has not been defined for this spectrum of tubal proliferations, they were characterized and separated immunohistochemically (10–13). In contrast to the early serous proliferaions, both type I and type II SCOUTs do not harbor mutations in *TP53*, but like early serous proliferations frequently exhibit loss of PAX2 expression (7). Type II SCOUTs have been distinguished further by strong staining for ALDH1 and β-catenin$^+$ (11,12).

As shown in this study, type II SCOUTs are defined by strong diffuse β-catenin$^+$. They are commonly encountered in the fallopian tubes and more commonly in women in the fifth decade or older (10). In this study, they were seen somewhat more frequently in women with gynecologic glandular neoplasia and in those with endometrioid neoplasia in the uterus but displayed a wide range of associations including women with no gynecologic epithelial neoplasia. Despite their association with some endometrioid neoplasms and the assumption that type II SCOUTs harbor CTNNB1 mutations, they have not previously been documented in continuity with diffusely

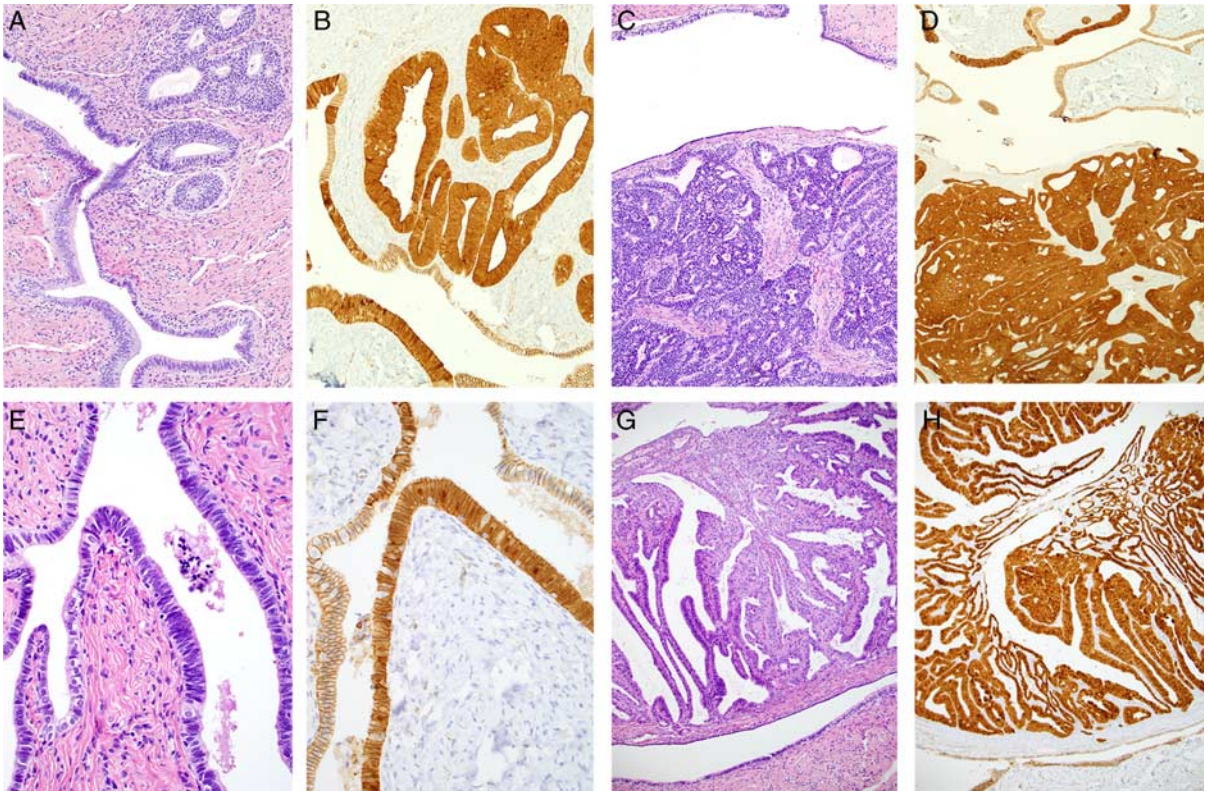

FIG. 3. Two cases with β-catenin$^+$+stem cell outgrowths (SCOUTs) and endometrioid adenocarcinomas of the same fallopian tube. (A and C) Hematoxylin and eosin–stained SCOUT/TEIN and endometrioid adenocarcinoma showing β-catenin$^+$. (B and D) In this case respectively (Case 14, Table 2) both uterus and both ovaries contained endometrioid adenocarciomas with normal (cytoplasmic) staining. An additional serous tubal intraepithelial carcinoma was discovered in the tube (not shown). (E and G) Hematoxylin and eosin–stained SCOUT and endometrioid adenocarcinoma in a second case (Case 15, Table 2), both β-catenin$^+$ by histochemistry. (F and H) This case also contained an endometrioid adenocarcinoma of the uterus with normal (cytoplasmic) staining for β-catenin.

β-catenin$^+$ endometrioid adenocarcinoma. Moreover, it has been well established that the diffuse β-catenin$^+$ that characterizes type II SCOUTs is not typical of most endometrioid carcinomas of the uterus or ovary that contain *CTNNB1* mutations (18).

Despite the lack of a direct relationship between type II SCOUTs and endometrioid adenocarcinomas in the female genital tract, there is evidence for an endometrioid carcinogenic sequence in the fallopian tube. One report of isolated endometrioid adenocarcinomas in the fallopian tubes of women with uterine endometrial carcinomas suggested that the 2 tumors are independent primary carcinomas and noted in situ components in some tubal tumors (24). However, lesions resembling type II SCOUTs were not described. Although the primary nature of tubal endometrioid carcinomas occurring in the setting of endometrial adenocarcinoma can be questioned, the report cited 2 others that reported tubal endometrioid adenocarcinomas associated with endometrial hyperplasia alone (25,26). Moreover, as shown in this study, in addition to type II SCOUTs, occasional β-catenin$^+$ lesions we classified as TEIN/atypical hyperplasia can be seen in the fallopian tubes, with gland crowding and squamous morules (Fig. 2). The role that type II SCOUTs might play in this process remains to be more precisely defined, but this study demonstrates that diffuse β-catenin$^+$, a feature uncommonly seen in conventional endometrioid adenocarcinomas, will distinguish not only type II SCOUTs, but also a subset of concurrent TEIN and/or tubal endometrioid adenocarcinomas. β-catenin$^+$ thus not only links these components in a putative carcinogenic sequence but also supports the independent origin of this unique subset of endometrioid carcinomas in the fallopian tube.

Although the juxtaposition of β-catenin$^+$ type II SCOUT, TEIN/atypical hyperplasia and tubal endometrioid adenocarcinoma supports a unique carcinogenic sequence, several questions remain. First, what is the frequency of tumors arising through this pathway? In our experience, most endometrioid carcinomas discovered in the fallopian tube are either not associated with type II SCOUTs or do not manifest with diffuse

β-catenin^{+} (D. Kolin and C. Crum, unpublished data). Second, are there germline genetic or acquired variables that influence risk of multiple endometrioid proliferations-or concurrent endometrioid and serous lesions in the fallopian tube? Third, are multiple lesions involving the fallopian tube and uterus clonally related, as has been proposed for endometrioid neoplasms in the uterus and ovaries (27)? These issues remain to be resolved and they underscore the need to further clarify the genetic and biologic underpinnings of multiple endometrioid neoplasms in the female genital tract.

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