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Do some epithelial ovarian cancers originate from a fallopian tube ciliate cell lineage?

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ABSTRACT

There is a general agreement that a large subpopulation of serous ovarian cancers arise from the fallopian tube mucosal epithelium. However, there is still some debate as to whether the cancers originate from a secretory or ciliate cell lineage. One well established method for determining the origin of a cell line is to document the expression of genes and proteins that are cell type specific. Lineage or tissue specific patterns of gene expression are evidence of direct decent from a given cell type within a tissue. It has recently been established that the Tumor Protein TAp73 gene (*TP73*) is expressed in basal epithelial cells that develop into multiciliate cells. *TP73* expression is therefore a marker for basal stem cells that are predestined to differentiate into cells with motile cilia and its expression is maintained in fully differentiated multiciliate cells. Interestingly *TP73* expression has also been observed in a high percentage of epithelial ovarian cancers. With this in mind, it is hypothesized that a high percentage of epithelial ovarian cancers which express *TP73* originate from a ciliate cell lineage.

Introduction

Ovarian cancer is relatively common in the female population with 22,000 newly diagnosed cases per year in the US and 14,000 related deaths, accounting for 1.3% of total cancer diagnoses and 2.4% of cancer related deaths. About 90% of ovarian cancers are epithelial carcinomas with serous ovarian cancers being the most common and lethal (Ovarian Cancer Research Fund Alliance) [1]. Worldwide, ovarian cancer ranks as the 7th most common cancer in women with an estimated 239,000 new cases diagnosed in 2012 (World Cancer Research Fund International).

Our understanding of the etiology of serous ovarian cancers has a long history of different empirically based hypotheses. The first credible hypothesis related to ovarian cancer development was based on the observation that factors which reduce the number of lifetime ovulations, such as pregnancy or use of ovulation blocking contraception, are protective. This relationship was first described by Fathalla as the incessant ovulation hypothesis [2]. The fact that the majority of ovarian cancers were initially thought to originate from the ovarian surface epithelium, together with the observed link to ovulation, led Ghahremani et al. to propose that the site of carcinogenesis was the lesions left within the ovary by follicle rupture [3]. In turn this led to a suggestion that epithelial cells lining the ovary surface, and those within invaginations of this lining that form cortical inclusion cysts, have an 'uncommitted' phenotype and can undergo a phenotypic change to Mullerian epithelium [4]. In turn, these cells were thought to give rise to serous ovarian cancers that originate from the ovarian epithelium. Recently, the distal fallopian tube has been recognized as the most likely source of early serous carcinomas, particularly in women carrying mutations within the BRCA1 and 2 genes that predispose them to the development of breast and ovarian cancer [5,6]. Currently, it is accepted that the majority of epithelial ovarian cancers, regardless of phenotype, may originate from Mullerian tissue fragments lining the female reproductive tract and the fallopian tube in particular [7]. There is evidence that these tissue fragments become fused to, or imbedded in, the ovarian surface and clefts that form at the sites of follicular rupture [8]. This is supported by the development of ovarian cysts containing columnar epithelium, which is often ciliated, as a procurer to cancer development, and has been reviewed by Kurman and Shih [9].

The fallopian tube and associated infundibulum epithelium primarily contains two different cell types, ciliated and secretory, that could give rise to serous ovarian cancers. Ciliated cells have

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motile cilia that aid in the movement of the egg released from the ovary to the uterus. The secretory cells have non-motile primary cilia that are thought to act as sensory structures [10]. By tracing patterns of gene and protein expression in ovarian tumors it may be possible to determine the cell type that contributes to the cancer's origin. This approach has previously been taken to demonstrate that *HOX* gene expression can be used to specify regional tissue identity within the female reproductive tract. In turn, *HOX* gene expression in various epithelial ovarian cancers has been used to identify the region of origin from within the female reproductive tract [11].

Hypothesis

Serous ovarian cancers that express the tumor protein TAp73 and other ciliogenesis associated proteins originate from a fallopian tube epithelium ciliate cell linage.

Supporting evidence

Link between TP73 expression, ciliate cells and ovarian cancer

The question of whether cells from the fallopian tube share cell specific markers with ovarian epithelial cancers is of utmost importance in determining the cellular origin of these cancers. Shared markers may indicate the cell type that is present in the fallopian tube epithelium from which serous ovarian cancers originate. One such marker is the protein TAp73. This protein is encoded for by the *TP73* gene which is closely related to the tumor suppressor gene *TP53*. There are two alternate transcripts produced from *TP73* that are translated into either a full length peptide (TAp73) or an N-terminus truncated peptide (ΔNp73) [12]. TAp73 has been long recognized as a modulator of TP53 in ovarian cancers [13,14] where it is expressed in a high proportion of tumors (up to88%) [15,16] and influences the sensitivity of ovarian cancers to chemotherapy [17,18]. This is particularly the case in BRCA1-deficient tumors [18].

Of special interest is the fact that TAp73 is regarded as a marker for ciliate cells and is expressed in ciliate cells of the fallopian tube [19]. TAp73 is also produced in ciliate cells as well as those without conspicuous cilia that are present within serous borderline tumors [19]. Recently Marshall et al. [20] have provided definitive evidence that TAp73 is present in the nuclei of not only multiciliate cells, but also in a subset of non-ciliate basal epithelial cells that differentiate into multiciliate cells. Using a *TP73* knockout mouse model these authors clearly demonstrated that mice homozygous negative for the *TP73* gene failed to produce ciliate cells within the fimbriae epithelium of the oviduct, mucosal epithelium of the middle ear and sinus, and the respiratory epithelium of the trachea and bronchiole. In addition, male mice negative for *TP73* produced sperm without flagellate tails. Marshal et al. [20] clearly demonstrated that *TP73* was expressed in all multiciliate cells in normal mice and, surprisingly, also in a population of non-terminally differentiated basal cells. The *TP73* expressing basal cells were capable of exiting the cell cycle, initiating centriole amplification and proceeding down a path of motile cilia production with terminal differentiation into multiciliate cells. They also demonstrated that that the murine pattern of *TP73* expression in the basal and multiciliate cells was the same in the airway epithelium in both mice and humans. These experiments clearly establish that multiciliate cells and their undifferentiated non-ciliate precursor cells express *TP73* and that expression of the TAp73 protein is a robust marker for the ciliate cell lineage.

CETN1: A human ciliogenesis gene expressed in ovarian cancers

Human *CETN1* and its encoded peptide, centrin1p, were first described by Errabolu et al. in 1994 [21]. *CETN1* is a retrogene located on human chromosome 18 and is thought to have originated via retrotransposition of mRNA transcribed from the *CETN2*, a ubiquitously expressed gene located on the X chromosome. In mice, where its expression is best characterized, *CETN1* is expressed in the testis during spermatogenesis and expression starts with the first wave of spermatogenesis, 14 days postpartum [22]. It is therefore regarded as a member of the spermatogenesis associated retrogenes which are intronless autosomal copies of housekeeping genes located on the X chromosome [23] that, through time, have acquired a predominantly testis specific pattern of expression. *CETN1* is also expressed in the retinal photoreceptor cells of all mammals where the encoded centrin1p peptide is localized to the connecting cilium [24]. In addition to *CETN1* and *2*, mammals carry two other autosomal copies of the CETN gene, *CETN3* which is ubiquitously expressed, and *CETN4* that is transiently expressed only in ciliated cells during ciliogenesis [25,26].

In humans the pattern of *CETN1* is different to that of other mammals. This is because in man *CETN4* has become nonfunctional and is recognized as an unprocessed pseudogene located on human chromosome 4 where it is designated as *CETN4P* on chromosome maps (Ensemble Genome Browser release 87). In mammals that have a functional copy of *CETN4* its expression is limited to ciliate cells. In mice the *CETN4* encoded peptide, centrin4p, localizes to the basal bodies of cilia [22]. *CETN4* is also expressed in the eye where the centrin4p peptide is localized to the basal body of the cilia that form part of the ciliary apparatus of the retinal photoreceptor cells [24]. In man, *CETN4* appears to have been, in part, functionally replaced by *CETN1* in cilia producing cells. Besides being expressed in the human eyes and testis [27], *CETN1* is also expressed in ciliated epithelium during cilia development and the centrin1p peptide localizes to the axoneme of the cilia or flagellum during differentiation of ciliated and flagellated cells [28].

Expression of several spermatogenesis associated retrogenes in ovarian cancers has previously been reported [29]. *CETN1* is a member of the spermatogenesis associated retrogenes and its persistent expression is normally limited to the testis as shown in Fig. 1. In contrast its X linked progenitor gene is highly expressed in all human somatic tissues as shown in panel B of Fig. 1. The primer pair that specifically identifies *CETN1* mRNA was used to screen 22 serous ovarian cancer samples obtained from the Wake Forest University Baptist Medical Center Tumor Bank. High levels of *CETN1* expression were observed in 17 of the samples with an additional four being positive for *CETN1* expression at a markedly lower level. These data would suggest that unlike normal cells undergoing ciliogenesis that transiently express *CETN1*, at least some cells within an ovarian cancer constitutively express *CETN1*. This combined with the fact that ovarian cancers also commonly express the ciliate cell marker TAp73, would suggest that genes involved in ciliogenesis are expressed in ovarian cancer and this may be a marker for their lineage of origin.

Ciliogenesis during the ovarian cycle

If we are to argue that ovarian cancers originate from a ciliate cell lineage located within the fallopian tube, there must be biological evidence that ciliogenesis is linked to the ovulation cycle and is associated with ciliate cell proliferation and differentiation. This is to fulfill the requirement of the hypothesis being consistent with Fathalla's incessant ovulation hypothesis that is generally accepted within the ovarian cancer research community [2]. Ciliogenesis during the human female menstrual cycle, first trimester of pregnancy and postpartum has been documented by Verhage et al.