CHAPTER

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Phenotypic Plasticity and the Origins and Progression of Ovarian Cancer

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INTRODUCTION

Cell plasticity—the ability for a cell to reversibly assume different phenotypes—is a common theme occurring throughout development, wound repair, and in cancer metastasis. It is often observed as an epithelial-to-mesenchymal transition (EMT), allowing an epithelial cell to acquire mesenchymal traits such as migration and invasion. This cell can then reassume its epithelial phenotype through a mesenchymal-to-epithelial transition, reacquiring epithelial characteristics such as stable cell-to-cell junctions to maintain the epithelial barrier. Previously, this transition was considered a binary process where a cell could be either epithelial or mesenchymal; however, recently, this transition has been thought of as a fluid transition, where cells can lie anywhere in the EMT spectrum and express combinations of epithelial and mesenchymal traits. The concept of stemness has now been affiliated with the EMT, where cells exhibiting mesenchymal characteristics often display stem cell traits, such as the ability to form spheres in vitro. Although it has become increasingly apparent that the mesenchymal state coincides with stemness, a cell committing too far into the mesenchymal state loses these stemness traits, suggesting there is a window along the EMT spectrum that coincides with optimal stemness properties.

Phenotypic plasticity may also reprogram the environment to promote cancer initiation and progression. Ovarian cancer is a heterogeneous population of cells also displaying this cellular plasticity. We discuss the contribution of plasticity to ovarian cancer progression in the context of metastasis, chemoresistance, cancer stem cells (CSCs), as well as immunosuppression. Cellular plasticity is necessary for many biological functions; however, it can also severely impact the efficacy of a cancer therapeutic. This chapter also discusses the potential of targeting this plasticity to complement current treatment strategies.

PHENOTYPIC PLASTICITY IN OVARIAN EPITHELIAL CELLS

The ovarian surface epithelium (OSE) is a poorly differentiated simple epithelium surrounding the ovary. It is composed of flat-to-cuboidal epithelial cells derived from the coelomic epithelium during embryonic development [1]. Initially, the OSE was not thought to play a role in ovarian physiology so remained understudied until the late 1980s to early 2000s when studies emerged implicating the OSE as a tissue of origin for ovarian cancer [1]. Since then, it has become well understood that the OSE is a layer of cells exhibiting both epithelial and mesenchymal characteristics, and the cells composing the OSE layer have the capacity to interchange between each phenotype in response to environmental cues [1,2]. The fallopian tube epithelium (FTE) is another accepted origin of ovarian cancer and is a layer of pseudostratified epithelial cells derived from the Müllerian duct [3]. Unlike the OSE, the FTE represents a differentiated epithelium composed of ciliated and secretory cells. The ratio of ciliated and secretory cells is known to shift from ciliated cell
dominance in the infundibulum to a secretory cell dominance in the isthmus [3]. This pattern of ciliated and secretory cells in the fallopian tube is not altered during the menstrual cycle, suggesting these cells comprise a more stable differentiated epithelium in contrast to the poorly differentiated OSE cells [3,4]. Ciliated FTE cells are not supported in cell culture conditions and over time result in a secretory FTE cell culture. Whether this is due to ciliated cells undergoing apoptosis or differentiating into secretory cells is unknown [5]. Taken together, the OSE represents a population of cells with the capacity to interchange between both epithelial and mesenchymal characteristics, whereas the FTE displays a more committed epithelial phenotype.

The ability to assume reversibly different cellular phenotypes has widely been studied in the context of an EMT, and the reverse mesenchymal-to-epithelial transition, during embryonic development, cancer metastasis, and wound repair. The epithelial state maintains tissue borders and acts as an epithelial barrier and the mesenchymal state allows for cellular migration and invasion for growth or repair of tissues [6–8]. During embryonic development, epithelial cells transiently acquire a mesenchymal phenotype to allow for cellular migration. Once the cells have reached their destination, they revert to their previous epithelial state. This has classically been studied in gastrulation, neural crest cell migration, and heart morphogenesis [8]. In the context of cancer metastasis, epithelial cancer cells assume a mesenchymal phenotype to allow for migration and invasion into neighboring tissues where they revert back to their epithelial phenotype to establish a metastatic site [9]. This epithelial-mesenchymal plasticity is also observed in wound repair. In the repair of an epithelial layer, cells assume a mesenchymal phenotype surrounding the injured site to allow for migration and secretion of new extracellular matrix proteins to close the wound and mediate a process referred to as reepithelialization [10]. The OSE layer also displays this plasticity where cells exhibiting an epithelial phenotype help maintain OSE structure and during ovulatory wound repair, these cells acquire a mesenchymal phenotype to repair the wound [1,2].

THE EPITHELIAL-TO-MESENCHYMAL TRANSITION

The EMT is the process of an epithelial cell acquiring the phenotype of a mesenchymal cell. This process was first described in the primitive streak of chick embryos by Elizabeth Hay in 1995 and defined as an epithelio-mesenchymal transformation [11]. This event was later reclassified as a transition to emphasize the reversibility of this process and to differentiate it from cell transformation, a process related to cancer initiation. During the EMT process, epithelial cells lose their apical-basal polarity and acquire a front-rear polarity [7,8,12]. Epithelial cell-cell junctions are lost and cell cytoskeletal reorganization occurs, resulting in the acquisition of a mesenchymal cell morphology [7,8,12]. Functionally, cells undergoing an EMT have enhanced migration and invasion and show resistance to apoptosis [8,12]. Gene expression changes commonly associated with an EMT include loss of CDH1 (E-cadherin), CLDN (Claudins), OCLN (Occludins), DSP (Desmoplakin), and PKP1 (Plakophilin) genes, all leading to a loss in epithelial barrier function [7]. Mesenchymal gene expression commonly gained during an EMT include CDH2 (N-cadherin), NCAM (Neural Cell Adhesion Molecule 1), and VIM (Vimentin), although specific genes can vary based on tissue type [7]. There have been several transcription factors (TFs) identified as master EMT-driving proteins such as the SNAIL family, basic helix-loop-helix, and ZEB family of TFs (ex: SNAIL, TWIST1, ZEB1, respectively) [7,8]. These traditional TFs are tightly regulated by mechanisms that have been evolutionarily conserved, highlighting their importance in normal cellular processes [13]. Additional TFs have been found to work in conjunction with the master EMT TFs such as Forkhead Box (FOX), GATA, and SRY Box (SOX) TF families [7]. Additional drivers of EMT have been studied, such as alternatively spliced mRNA of genes such as Cluster of Differentiation (CD) 332 and p120-catenin and noncoding RNAs (microRNAs and long noncoding RNAs) such as miR-34 and H19, respectively [14–17]. With the emergence of high-throughput techniques, such as RNA-Seq and ChIP-Seq, more complex regulation of the EMT process is being uncovered and increasingly more interactions being identified as regulators of this program.

Recently, many studies have demonstrated that the EMT is best represented by a spectrum with the epithelial phenotype at one end, the mesenchymal phenotype at the other end, and a range of intermediate, or partial EMT in between [6–8,18]. In the intermediary states, also referred to as “metastable” states, cells can possess varying levels of both epithelial and mesenchymal traits [6]. Huang et al. used 43 ovarian cancer cell lines to demonstrate the range of EMT states [19]. Using EMT-related gene expression, they classified these tumor cell lines into 4 categories: epithelial, intermediate epithelial, intermediate mesenchymal, and mesenchymal represented by 20.9%, 41.9%, 18.6%, and 18.6% of cell lines, respectively [19]. They found that different EMT-TFs peaked in expression levels in these categories, suggesting these EMT-TFs have different weights in dictating where the cell line falls within the EMT spectrum [19]. The next year, Tan et al. developed an EMT scoring method using gene expression profiles of a variety of cancer cell types to estimate quantitatively where a particular tumor or cell line falls.
within this EMT spectrum [20]. Most recently, Jolly et al. introduced the concept that the EMT spectrum is multidimensional and different EMT modulators contribute to different EMT characteristics on this spectrum. For example, the EMT characteristics migration and invasion can be represented as different branches on the EMT spectrum and are regulated by different sets of EMT-TFs [21]. Taken together, it is becoming increasingly apparent that the EMT is a fluid state regulated by numerous factors, and cells have the capacity to shift their positioning on the spectrum based on their environmental cues (Fig. 1A).

THE EPITHELIAL-TO-MESENCHYMAL TRANSITION AND STEMNESS

To further the EMT spectrum complexity, it has been demonstrated that cells undergoing an EMT acquire stem cell characteristics (stemness) [22–25]. Mani et al. were the first to publish this finding in 2008 using nontransformed cells [22]. Immortalized human mammary epithelial cells induced to undergo an EMT via Transforming Growth Factor Beta-1 (TGFβ1) treatment or using ectopic expression of TWIST or SNAIL were found to acquire stem cell marker expression and increased mammosphere formation, which are two characteristics of stem cells [22]. Guo et al. further characterized this phenomenon using transient ectopic expression of Slug (another EMT-TF), showing these stem cells were functional in vivo in a mammary gland reconstitution assay [23]. This efficiency was enhanced when another EMT-TF commonly associated with stemness, Sox9, was also expressed [23]. This study suggests that regulators of EMT can drive this stemness phenotype synergistically [23]. In 2015, Schmidt et al. showed that constitutive Twist1 expression induced an EMT in mammary epithelial cells; however, transient expression was required to promote stemness [25]. The authors observed that removal of Twist1 did not fully restore cells to an epithelial state (mesenchymal-to-epithelial transition, MET), but maintained cells in a partial EMT state where they were “primed” for stemness, suggesting there is a window of stemness within the EMT spectrum [25]. This concept has also been inferred by Jolly et al. using a theoretical modeling of an EMT where both limits of the EMT spectrum have cells exhibiting less stemness than the intermediate zones [26]. The authors further elaborated upon this idea by showing that the positioning of the window of stemness on the EMT spectrum is not universal for all cell types and this positioning can be set using EMT driving factors, but “fine-tuned” using

![Diagram](image)

**FIG. 1**  (A) A schematic of the epithelial-mesenchymal transition, highlighting a continuous transition from an epithelial to a mesenchymal state, along with characteristics associated with each state. (B) Two models of the relationship between stemness and morphological characteristics associated with an EMT. Historically, these traits have been thought to correlate quite strongly (left model); however, recent work suggests that stemness is often optimal in an intermediate state, which may be context-dependent (“window of stemness” model; right). EMT, epithelial-to-mesenchymal transition; MET, mesenchymal-to-epithelial transition.

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modulating factors such as OVOL. OVOL couples with traditional EMT-driving factors to inhibit a full mesenchymal phenotype but simultaneously enhances the stemness phenotype [27]. This concept of a stemness window within the EMT spectrum has been shown in ovarian cancer cell lines where those in an intermediate EMT state possess enhanced spheroid formation and are anoikis resistant, both stemness characteristics [19]. Taken together, it appears that within the EMT spectrum there is a window of stemness whose specific location is modulated by EMT-driving factors that work together to regulate where this window lies (Fig. 1B).

**STEMNESS IN THE OVARIAN SURFACE EPITHELIUM**

Identification and Characterization of Stemness

OSE cells are thought to contain a stem cell population that is present to maintain tissue homeostasis [28]. Since 2008, several studies have evaluated common stem cell characteristics to identify this population of cells. DNA label retention has been used to identify slow-cycling somatic stem cells that exhibit asymmetric division and retain a label for long periods of time. In comparison, lineage-committed daughter cells (which proliferate more rapidly) dilute out the label as they proliferate. Szotek et al. were the first to report a population of stem-like mouse OSE cells using this technique [29]. Side population analysis is another common technique used to identify a population of stem cells and can be identified using the ATP-binding cassette (ABC) pump inhibitor, Verapamil. ABC pumps are abundant in stem cells and are therefore able to efflux dyes such as Hoechst dye efficiently, whereas differentiated cells have a limited ability to do so. Szotek et al. found their population of label-retaining cells was enriched when isolating the side population present in mouse OSE cells [29]. The following year, Bowen et al. published microarray and immunohistochemical data of human OSE cells, showing activation of stem cell quiescence and regulation pathways as well as expression of stem cell markers within these cells, suggesting these putative stem cells exist in both mouse and human ovaries [30]. From 2012 to 2014, several publications further characterized this stem cell population in both mouse and human using in vitro assays such as sphere formation, and in vivo assays such as lineage tracing and label retention [31–35]. There have even been reports of OSE stem-like cells with the capacity to differentiate into additional cell types, including oocyte-like structures [36–41]. Although many studies have identified stem cell characteristics in the OSE, there has yet to be a consensus on which marker(s) accurately represent this population of cells. One possible reason for this discrepancy in stemness markers, maybe that the OSE does not have a fixed stem cell population but a transient one, that can be induced or expanded based on environmental cues.

Regulation of OSE Stemness

Isolating OSE stem cells based on their gene expression may enrich for stem cell characteristics; however, there has not been any demonstration that combining stem cell marker expression purifies this population of cells, like it does in the hematopoietic system—a hierarchical stem cell model. This suggests the OSE stem cell population is best represented as a state rather than a defined population of cells, where these cells have the capacity to interchange between a “less differentiated state” exhibiting stem cell characteristics and a “more differentiated” cell state exhibiting more committed epithelial cell characteristics. Gamwell et al. showed that culturing mouse OSE cells negative for a stem cell marker Stem Cell Antigen 1 (Sca1/Ly6a) revert back to a Sca1-positive state, a marker of cells exhibiting stem cell characteristics, exemplifying the plasticity of this cell state [31]. Furthermore, the authors found that treating mouse OSE cells with TGFB1 (a known EMT inducer) increases stem cell characteristics, such as sphere formation and stem cell marker expression in vitro, indicating this cell state is regulated by factors such as those driving an EMT. Studies examining EMT regulation and the stemness phenotype in OSE are summarized in Tables 1 and 2.

To this date, there have not been any direct studies in the OSE relating EMT and stemness, but this relationship has been established in other tissues as described above. As there is no agreement or coordination of stemness markers in the OSE, but there are clear stem cell phenotypes, perhaps the window of stemness is best represented by adding a second dimension to the EMT spectrum, where cells lie within the EMT spectrum based on their epithelial/mesenchymal genes, and are shifted into the stemness dimension based on their stemness gene expression. This theory would allow for cells to exhibit similar functional readouts, while expressing different genes and would explain the discrepancy in some experimental findings (Fig. 1B).

**STEMNESS IN THE FALLOPIAN TUBE EPITHELIUM**

Like the OSE layer, the FTE is also thought to contain a stem cell population that is present to maintain tissue homeostasis, although less is known about this population of cells. Wang et al. identified a population of label
**TABLE 1** Overview of EMT/MET Regulation in OSE and FTE Cells

<table>
<thead>
<tr>
<th>Cell type</th>
<th>In vitro/in vivo</th>
<th>Species</th>
<th>Treatment</th>
<th>EMT/MET characteristics</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [primary culture]</td>
<td>Epidermal growth factor [EGF]</td>
<td>Mesenchymal morphology&lt;br&gt;↑ Motility&lt;br&gt;↑ Secretion of promatrix&lt;br&gt;metalloproteinases&lt;br&gt;↑ ERK, ILK, AKT, and GSK-3 signaling</td>
<td>[142]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [immortalized cells]</td>
<td>Exogenous E-cadherin expression</td>
<td>Epithelial morphology&lt;br&gt;↑ Adherens and tight junctions&lt;br&gt;↑ Keratin expression</td>
<td>[143]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [primary culture]</td>
<td>EGF + hydrocortisone</td>
<td>Mesenchymal morphology&lt;br&gt;↑ Keratin expression&lt;br&gt;↑ Collagenous extracellular matrix</td>
<td>[144]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [primary culture]</td>
<td>Bone Morphogenetic Protein 4 Noggin</td>
<td>No change in cell motility</td>
<td>[145]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [primary culture]</td>
<td>TGFβ1</td>
<td>Prevented formation of epithelial barrier&lt;br&gt;↑ E-cadherin, Claudin 1, Occludin, Crumbs 3&lt;br&gt;↑ Snail, N-cadherin, Slug</td>
<td>[146]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>Exogenous Pax8 expression</td>
<td>Mesenchymal morphology&lt;br&gt;↑ Migration&lt;br&gt;↑ N-cadherin and Fibronectin</td>
<td>[147]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [primary culture]</td>
<td>Collagen gels</td>
<td>Mesenchymal morphology</td>
<td>[148,149]</td>
</tr>
<tr>
<td>FTE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>Pax8 knockdown</td>
<td>No changes in migration or apoptosis</td>
<td>[147]</td>
</tr>
<tr>
<td>FTE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>TGFβ1</td>
<td>Mesenchymal morphology&lt;br&gt;↑ Migration&lt;br&gt;↑ Snail and ↓ E-cadherin</td>
<td>[45]</td>
</tr>
</tbody>
</table>

EMT, epithelial-to-mesenchymal transition; FTE, fallopian tube epithelium; MET, mesenchymal-to-epithelial transition; OSE, ovarian surface epithelium; TGFβ1, Transforming Growth Factor Beta-1.

**TABLE 2** Overview of the Regulation of OSE and FTE Stemness

<table>
<thead>
<tr>
<th>Cell type</th>
<th>In vitro/in vivo</th>
<th>Species</th>
<th>Treatment</th>
<th>Stemness characteristics</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Human [primary culture]</td>
<td>Follicular fluid</td>
<td>Formation of primitive oocyte-like cells positive for alkaline phosphatase and markers of pluripotency [SOX2, SSEA4, OCT4A, NANOG, NANOS, STELLA, CD9, LIN28, KLF4, GDF3, and MYC]</td>
<td>[150]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>Follicular fluid&lt;br&gt;TGFβ1&lt;br&gt;LIF</td>
<td>↑ Stem cell marker expression [Scal]&lt;br&gt;↑ Proliferation, ↑ sphere formation, ↑ Scal expression, converts SCA1+ to SCA1− cells&lt;br&gt;↑ Sphere formation, ↓ Scal expression</td>
<td>[31]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vivo</td>
<td>Mouse</td>
<td>Ovulation</td>
<td>Label retaining cells [stem cells] are proliferative postovulation</td>
<td>[29]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vivo</td>
<td>Mouse</td>
<td>Ovulation</td>
<td>Ovulating OSE regions exhibit mitotically active LGR5+ cells [stem cells]&lt;br&gt;LGR5+ cells respond to local Wnt signals</td>
<td>[33]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vivo</td>
<td>Mouse</td>
<td>miR-34 family and miR-376b</td>
<td>↓ in the stem cell population [ALDH+ cells]</td>
<td>[32]</td>
</tr>
<tr>
<td>OSE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>Exogenous Pax2 expression</td>
<td>↓ Sphere formation and stem cell marker expression [CD44, Scal, Lgr5]</td>
<td>[45]</td>
</tr>
<tr>
<td>FTE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>Serum</td>
<td>Label retaining cells ↑ expression of endometrial, proximal, and distal oviductal specific genes</td>
<td>[42]</td>
</tr>
<tr>
<td>FTE</td>
<td>In vitro</td>
<td>Mouse [primary culture]</td>
<td>TGFβ1</td>
<td>↑ Stem cell marker [CD44 expression]</td>
<td>[45]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Pax2 knockdown</td>
<td>↑ Stem cell markers [CD44, Scal, CD133] ↑ sphere formation</td>
<td>[45]</td>
</tr>
</tbody>
</table>

FTE, fallopian tube epithelium; OSE, ovarian surface epithelium; TGFβ1, Transforming Growth Factor Beta-1.
retaining cells located in the epithelium of the distal end of the mouse fallopian tube (oviduct) [42]. These cells formed spheres in vitro and were able to differentiate into glandular structures expressing mature Mullerian epithelial cell markers [42]. The ability of these cells to contribute to FTE homeostasis was not assessed, but these cells were able to be differentiated into cell lineages of the endometrium, proximal and distal oviduct [42]. Paik et al. identified a population of stem-like cells in the distal end of the human fallopian tube expressing stem cell markers [43]. These cells also had sphere forming potential, suggesting this population of stem-like cells exists in the human fallopian tube as well [43]. Patterson and Pru also demonstrated label retention in the distal end of the mouse oviductal epithelium [44]. Additionally, there has been a population of cells exhibiting stem cell characteristics located at the hilum region of the mouse ovary, where the OSE and oviductal epithelium meet, that is, slow cycling expresses stem cell markers and is capable of sphere formation [32]. Additional stem cell markers have been found in the distal end of the mouse oviductal epithelium, such as Lgr5 [33]; however, further characterization of these cells and their regulation has not been assessed. Recently, a study showed that the stem cell characteristics in the oviductal epithelium can be enhanced with Pax2 knockdown or TGFβ1 treatment, which works in part by decreasing Pax2 expression [45]. This study directly implicates an EMT with the acquisition of stemness in the oviductal epithelium.

Recurrent discoveries indicate that stem cell properties evolve over time. To get a sense of the field’s trajectory, we’ve constructed a timeline of publications describing putative stem cell populations of the ovarian and fallopian tube/oviductal epithelia. The field experienced a burst of activity between 2012 and 2014; however, this has been followed by several years of inactivity.

PHENOTYPIC PLASTICITY IN OVULATORY WOUND REPAIR

Ovulation, the process where the mature oocyte leaves the ovary for fertilization in the fallopian tube, is a cyclic process that is composed of three stages: the preovulatory, ovulatory, and postovulatory phases [28]. In the preovulatory phase, the dominant follicle continues to
develop to the antral or Graafian stage where it is ready for ovulation. During this development, the follicle size is dramatically increased producing a stigma in the ovarian tissue surrounding the follicle. In the events leading up to ovulation, the OSE layer surrounding the stigma proliferates to accommodate this change in ovarian size, whereas the OSE cells surrounding nonovulating sites remain nonproliferative [46,47]. Ovulation is triggered by a surge in luteinizing hormone (LH). The LH surge induces OSE cells to produce proteases, such as urokinase-type plasminogen activator, which activates a proteolytic cascade that degrades extracellular matrix proteins and induces apoptosis at the apex of the ovarian stigma [48]. This epithelial cell breakdown facilitates the rupture in the OSE layer, allowing for ovulation to proceed. Once the cumulus-oocyte complex is released from the tissue surrounding the follicle. In the events leading up to ovulation, the OSE layer surrounding the stigma proliferates to accommodate this change in ovarian size, whereas the OSE cells surrounding nonovulating sites remain nonproliferative [46,47]. Ovulation is triggered by a surge in luteinizing hormone (LH). The LH surge induces OSE cells to produce proteases, such as urokinase-type plasminogen activator, which activates a proteolytic cascade that degrades extracellular matrix proteins and induces apoptosis at the apex of the ovarian stigma [48]. This epithelial cell breakdown facilitates the rupture in the OSE layer, allowing for ovulation to proceed. Once the cumulus-oocyte complex is released from the ovary, the ovulatory wound is repaired in as little as 12h in mice [47,49].

Reepithelialization

Wound repair is a complex event that requires synergy of multiple components to be successful. Reepithelialization is one step in this process where cells on the edge of the wound site migrate to reestablish the damaged epithelium [6]. After ovulation, OSE cells surrounding the wound site continue to proliferate and assume a mesenchymal phenotype allowing for the secretion of collagen and extracellular matrix proteins [48]. Cell plasticity is also important for reepithelialization of the OSE layer. OSE cells need to assume a mesenchymal morphology to facilitate the repair, however, require the ability to reestablish their epithelial phenotype once the repair is completed to form the epithelial barrier. Recently, studies in the skin have shown that a partial EMT is induced during wound repair [10]. This transient reprogramming of the wound edge cells facilitates their migration and invasion into the wound site as a cohesive cohort and not as individual cells [8]. During this transient reprogramming, intermediate filaments are retracted, breakdown of the basement membrane occurs, and epithelial cells lose their polarity. Once cell migration has taken place, these cells reform their cell-substrate contacts [50]. During this repair process, cells maintain their cytokeratin expression and desmosomes, further implying these cells undergo a partial EMT [8]. This partial EMT can be seen in the OSE cell layer, which maintains expression of keratin 8 and E-cadherin throughout ovulatory wound repair [51].

During ovulatory rupture, follicular fluid from the antral follicle bathes the OSE layer surrounding the rupture site. A recent study assessed the composition of human follicular fluid and found proteins belonging to several functional groups such as insulin growth factor (IGF) and IGF-binding protein families, growth factors and related proteins, receptor signaling, defense/immunity, antiapoptotic proteins, matrix metallopease-related proteins, and complement activity [52]. The authors found that once ovulation is induced (following human chorionic gonadotrophin treatment), the composition shifted to include more proteins belonging to the protease inhibition, inflammation, and cell adhesion families [52]. Many of these follicular fluid components are known inducers of an EMT such as TGFB1 and IGF. These components may help facilitate the transient reprogramming to an EMT state to aid in wound repair.

OSE undergoing reepithelialization around the wound site also gain expression of the stem cell marker Lgr5, suggesting this partial EMT allows for reepithelialization and also induces stemness, necessary to maintain homeostasis [33]. Furthermore, Gamwell et al. showed that treating OSE cells with follicular fluid enhances their stem cell characteristics, suggesting ovulatory wound repair expands this population [31]. The concept that ovulation changes the OSE stem cell profile partially explains why there has not been agreement in the gene markers for this population of cells. Different factors produced in the surrounding ovarian tissue interact with the OSE layer to promote this stem-like state to maintain tissue homeostasis. Since these factors are complex and transient within the ovary, it is not probable that one marker of stemness will be found that represents all stem cells, but it is possible to describe these cells as a state within the spectrum.

Inflammation

Another important player in wound repair is the immune system. In adult tissues, wound repair relies heavily on a functional immune response. Wound repair is hindered when the immune response is impaired [10]. For example, inhibiting macrophage function has been shown to delay tissue repair in rabbits and mice [53,54]. Inflammation occurring after an epithelial wound recruits primarily neutrophils and macrophages to the wound site, which work together to clear the wound debris [10]. In the ovary, these immune cells home to the forming corpus luteum after ovulation in the mouse, rat, and human [55–57]. Inflammation also supports reepithelialization through the secretion EMT-driving factors such as TGFB1 and tumor necrosis factor (TNF) alpha, which act on the epithelial cells surrounding the wound site [10,58,59]. As mentioned above, human follicular fluid also becomes more inflammatory at ovulation, suggesting follicular fluid contributes to the inflammatory response [52]. Taken together, inflammation occurring during wound repair is important to facilitate this repair by altering the ovarian niche to be more inflammatory and promote an EMT in the repairing epithelium.
Potential Consequences of Cell Plasticity

Ovulation is a cyclic event, occurring once every 28 days in women of reproductive age. It is also the primary nonhereditary risk factor for ovarian cancer, with the number of ovulatory cycles being proportional to ovarian cancer risk [60]. This suggests that ovulation, or ovulatory wound repair, can lead to ovarian cancer initiation. During each cycle, the repairing OSE layer proliferates and undergoes a partial EMT. During this time, the cells surrounding the wound site also interact with the inflammatory agents present in the follicular fluid. Cells exhibiting a mesenchymal phenotype display resistance to apoptosis and therefore can survive harsh environmental conditions; however, this cell survival may allow the accumulation of DNA damage over time. Murdoch and Martinchick assessed the surviving OSE cells surrounding the ovulatory rupture site and found 8-oxoguanine modifications in these cells, indicating DNA damage [61]. As these cells are undergoing an EMT also have enhanced stemness characteristics, it is conceivable that these cells may develop DNA mutations that are propagated over time and can lead to ovarian cancer initiation.

The inflammation accompanying wound repair is tightly regulated since its dysregulation could have severe consequences. Improper wound repair in other tissues such as the liver, kidney, and lung results in tissue scarring and fibrosis, leading to chronic inflammation [6]. This chronic inflammation results in persistent secretion of EMT-driving factors and maintenance of the EMT state in the epithelium [12]. As EMT is related to stemness characteristics, chronic inflammation in the ovary would also increase the stem cell characteristics in the OSE and distal FTE, which over time could transform into a cancer initiating cell. Briley et al. reported that fibrosis in the mouse ovary increases with age and number of ovulatory cycles [62]. Although this has yet to be established in humans, ovarian fibrosis is known to be associated with reduced fertility in women with polycystic ovarian syndrome [63]. It is possible that fibrosis in the human ovary increases with age and the associated chronic inflammation could promote both an EMT and stemness in the OSE and FTE. This combination of events theoretically could provide a microenvironment conducive to cell transformation and the development of neoplastic lesions. This hypothesis could help to explain why the median age of ovarian cancer detection is postmenopausal, after the age-associated accumulation of postovulatory repair events results in ovarian fibrosis and inflammation [60].

The FTE is another site of origin for ovarian cancer, and is also affected by ovulation. The follicular fluid that is expelled from the ovary comes into contact with the distal FTE cells. Like in the OSE layer, the follicular fluid components may drive an EMT phenotype, induce DNA damage, and promote stemness in the FTE. This concept is supported by Alwosaibai et al. who found that treating FTE cells with TGFβ1, a component of follicular fluid, induced an EMT and increased the expression of stem cell markers [45]. Interestingly, these effects were mediated in part by downregulation of Pax2, a transcription factor commonly lost in serous tubal intraepithelial carcinomas, a precursor lesion for ovarian cancer. Furthermore, King et al. detected proinflammatory macrophages in the oviduct of superovulated mice as well as increased levels of phospho-gH2A.X, a marker of DNA damage, in the oviductal epithelial cells [64]. Taken together, the plasticity exhibited during wound repair by both the OSE and FTE layers may enable wound repair to take place and work to maintain tissue homeostasis. Under the inflammatory conditions of wound repair, however, it may change the ovarian niche to result in more DNA damage and promote transformation.

Heterogeneity of Ovarian Cancer

There are many different types of ovarian cancer, each characterized by distinct histological and molecular characteristics [65,66]. Much of the variation between these subtypes is generally accepted to be due to differences in the cancer’s cell-of-origin or specific genetic aberrations [67,68]. For example, there is evidence that endometrioid ovarian cancer is derived from endometrial tissue of atypical endometriosis, while high-grade serous carcinoma (HGSC) is thought to originate from either the FTE or OSE, and HGSC are often associated with TP53 mutations, whereas low-grade carcinomas are not [67,68].

Over the last decade, advances in large-scale genomics have enabled interrogation into the variation that exists across tumors of the same histological subtype. The Cancer Genome Atlas profiled the transcriptome of 489 HGSC tumors and noted that the tumors fell into four distinct clusters: differentiated, immunoreactive, mesenchymal, and proliferative—each named for the gene expression patterns that define the cluster [69]. A study by Tan et al. [70] further refined this classification by including gene expression data sets from over 2500 additional tumor samples to their analysis and once again found that tumors were members of distinct molecular subtypes. The expression patterns associated with each subtype resembled the clusters previously defined by The Cancer Genome Atlas, but were largely driven by the epithelial-, mesenchymal-, or stem cell-associated gene expression patterns, so they were named Epi-A, Epi-B, Mes, Stem-A, and Stem-B [70]. Importantly, both studies found that the molecular subtype of the group can impact clinical outcomes. For example, the Stem-A and Epi-B classifications were shown to be prognostic factors, independent of other factors, such as tumor stage.
Additionally, the efficacy of various treatments can be dependent on the molecular subtype: Stem-A tumors are particularly susceptible to microtubule assembly inhibitors [70], while Mes tumors are selectively susceptible to inhibition of the receptor tyrosine kinase AXL [71].

While it is evident that ovarian tumors of the same histological subtype can be quite heterogeneous, and that this contributes to tumor progression and patient prognosis, the source of this heterogeneity is not clear. All molecular profiling used to define these subtypes has relied on technologies that make measurements from bulk populations of cells (e.g., a tumor core), and as a consequence, are sensitive to differences in the cellular composition of the tumor. For example, a recent study found that the mesenchymal and immunoreactive classifications from The Cancer Genome Atlas can likely be attributed to tumors with a higher stromal content, rather than a unique expression signature from the carcinoma cells themselves [72]. However, while defining the Epi-A, Epi-B, Mes, Stem-A, and Stem-B subtypes from tumor samples, Tan et al. also found that cultured ovarian cancer cell lines, which are likely relatively pure cancer cell populations, could also be clustered into these five subtypes while maintaining a relatively high correlation with expression profiles from tumor samples of the same subtype [70]. This suggests that while the tumor microenvironment can certainly contribute to the variation between molecular profiles, the carcinoma cells themselves can also be phenotypically diverse. What is not clear is how this diversity arises. It is possible that these cells arise from a different cell-of-origin; however, there are only two putative sources of HGSC—the FTE and OSE (or inclusion cysts derived from them)—which does not account for the diversity of molecular subtypes. It could also be that tumors of the same subtype share a common mutational profile that may drive the particular phenotype, but this has yet to be shown.

What seems likely is that the cancer cells are transcriptionally and epigenetically programmed by tumor microenvironment throughout their initiation and progression, driving this phenotypic diversity. As discussed previously in this chapter, normal ovarian epithelial cells are quite plastic and readily shift between epithelial and mesenchymal phenotypes to maintain tissue homeostasis, so it seems likely that ovarian carcinoma cells retain this property. Unfortunately, evidence of ovarian carcinoma cell plasticity in vivo is sparse, and much of the work to support this hypothesis has been demonstrated with ovarian cancer cell lines in vitro. However, over the last 14 years, since the earliest studies exploring the relationship between the EMT and ovarian cancer progression, there has been an accumulation of several hundred studies that explore the factors that drive this phenotypic shift.

The key drivers of the EMT in ovarian carcinoma cells seem to be largely conserved across other normal and cancer cell types. The classic EMT-TFs SNAI1 and SLUG were the first factors shown to induce an EMT in ovarian cancer cells [73]. Their ectopic expression in a cultured HGSC cell line induced the morphological traits of an EMT, as well as enhanced their ability to migrate and invade through a matrigel substrate in vitro [73]. Soon after, TWIST1 [74], TWIST2 [75], ZEB1 [76], and ZEB2 [76,77] were each implicated to have similar roles. Many of the published studies in this field have focused on specific components of the signaling pathways that induce an EMT and have found commonalities with other epithelial tissues and tumors. Receptors and kinases of many of the major signaling pathways, including the TGFB [78], WNT [79], PI3k-AKT [80], ERK [81], and JAK/Stat pathways [81], have been shown to induce an EMT in ovarian carcinoma cells. Additionally, several microRNAs and long noncoding RNAs have been shown to modulate the expression of EMT TFs. The miRNA-200 family [76, 125a [82], 429 [83], 187 [84], 29b [85], 101 [86], 7 [87], 150 [88], 506 [89], 373 [90], 186 [91], 153 [92], 203 [93], 1181 [94], 31 [95], 30d [96], 382 [97], 340 [98], 125b [99], 137 [100], and 34a [100] each have been shown to inhibit an EMT in ovarian cancer cells, whereas only miRNA-181a [101], 23a [102], 186 [91], and 21 [103] have been shown to induce one. Many of these microRNAs have been shown to function directly through targeting the transcripts of the classic EMT-TFs. Less is known about long noncoding RNAs in ovarian cancer; however, HOTAIR has been shown to induce an EMT [104], while the noncoding HOXA11-AS prevents the transition [105].

It is interesting to appreciate the imbalance of factors that drive cells along the epithelial-mesenchymal continuum: there seem to be far more TFs and signaling molecules that actively push cells to be more mesenchymal rather than epithelial. Similarly, there seem to be more microRNAs, which are typically repressive in nature, that make cells more epithelial. Perhaps this is a bias in research (e.g., labs research EMT more than MET), or perhaps this suggests that the regulatory systems positioning cells along the epithelial-mesenchymal continuum are not two opposing gene networks (EMT vs MET programs), but rather a single, tunable gene network, and the phenotype of each cell is defined by degree of its activity.
expression. Consistent with other EMT literature, most describe the cells’ increased ability to migrate in vitro using scratch-wound assays and increased invasion through an extracellular matrix (e.g., matrigel). It has long been thought that undergoing an EMT is critical for cancer cells to break from the primary tumor, invade through adjacent tissue, and metastasize throughout the body [106]. In fact, modulating the EMT status of ovarian carcinoma cells does seem to affect metastasis in xenograft models. For example, knockdown of SNAIL in an ovarian cancer cell line led to a near-complete inhibition of metastasis in an orthotopic mouse model [107]. In this same model, SNAIL expression also tended to be higher in metastatic tumors than primary ovarian tumors [107].

Recently, the EMT-metastasis hypothesis has been met with criticism, largely because findings have hinged on experimentally inducing or inhibiting the EMT. So while more-mesenchymal cells seem to have an enhanced ability to metastasize, it is not clear if carcinoma cells dynamically activate an EMT to facilitate metastasis, or to what extent the EMT-associated genes are required to allow metastasis to occur. Two recent studies published in Nature used conditional knockouts or genetic lineage tracing, fluorescently labeling cells upon the expression of EMT-TFs, to demonstrate that the cells of metastases from breast [108] and pancreatic [109] cancer mouse models had not undergone an EMT. However, these studies are not without their own limitations. The genetic manipulations in both studies were limited to a small number of EMT-associated genes. Knockout of a single EMT-TF may not be sufficient to block the metastasis component of an EMT in this model, and lineage tracing based on a single gene may not capture all cells that had undergone an EMT. However, Fischer et al. [108] also demonstrated that overexpression of miR-200, which inhibits the expression of multiple EMT genes, still failed to affect metastasis, further supporting that at least in some contexts, the EMT may be dispensable in metastasis.

In ovarian cancer models, there has not been much focus on tracking cells throughout the process of metastasis, and most EMT-metastasis studies have relied on overexpressing or knocking down gene expression. Rafehi et al. did find that ovarian cancer cells, when switched from adherent culture to spheroid culture in suspension, had elevated expression of mesenchymal-associated genes, and mostly restored epithelial gene expression when placed back in adherent culture conditions [110]. The ability for the cells to grow in suspension was also reduced when the cells had been exposed to a TGFβ signaling inhibitor. While this is consistent with cells undergoing an EMT when transferred to suspension culture, it is also possible that this is not a dynamic response, but rather, the process is simply selective for cells that already had a more-mesenchymal phenotype. However, the ability to restore epithelial gene expression when the spheroids were transferred back to adherent culture is supportive of dynamic plasticity, rather than selection of static cell populations.

Chemoresistance

Another cancer-associated trait modulated by the EMT is sensitivity to platinum-based chemotherapy—a prevalent issue across a variety of cancers [111]. Many of the studies that identified regulators of the EMT in ovarian cancer also implicated these factors in promoting chemoresistance. The EMT-inducing TWIST1 [112], STAT3 [113], FOXM1 [114], and more, each endow ovarian carcinoma cells with an increased resistance to cisplatin, whereas miRNA-186 [91] and KLF4 [115]—each of which induces an MET—render cells more sensitive to cisplatin. Given this, therapeutically targeting the EMT seems like a logical strategy to sensitize ovarian carcinomas to chemotherapy [116–118]. Interestingly, these findings are all confounded by one large study that performed gene expression microarrays on 46 human ovarian cancer cell lines [119]: each cell line was assigned a binary classification of “epithelial” or “mesenchymal,” and was assessed for sensitivity to cisplatin, and the gene expression changes that occurred in response to a 48-h exposure to a cell-line-specific GI50 dose [119]. They surprisingly found that epithelial-classified cell lines were less sensitive to cisplatin than the mesenchymal lines, with a higher GI50 dose on average and a reduced apoptotic response [119]. The authors mention that this finding may be the result of differences in “acquired” and “inherent” EMTs; however, these findings have yet to be consolidated with the immense body of work relating an EMT phenotype with resistance to chemotherapy.

Cancer Stem Cells

Related to the chemoresistant trait is the notion of CSCs. It has been hypothesized that, like in tissue development, the cells comprising tumors are hierarchically organized, with self-renewing stem cells populating the tumor through cell division and subsequent differentiation of daughter cells [120]. A logical extension is that not all tumor cells are equally capable of forming new tumors. In fact, in many types of cancer, it has been demonstrated that cells with certain gene expression signatures are more capable of forming tumors in xenograft models than cells lacking the given signature. While limiting dilution xenograft tumor models are currently the gold standard for assessing this phenotype, the ability to form clonal, self-renewing spheroids in suspension culture is the most commonly used proxy for this trait. Additionally, resistance to chemotherapy is a feature of CSCs,
attributed to the expression of ABC transporters, enhanced DNA damage response, and more [121]. In ovarian cancer, the expression of several marker genes, albeit in different combinations in different studies, has been attributed to putative CSCs, including CD44, CD24, CD133, ALDH1, CD117, and EPCAM [122].

In the first study that demonstrated that the EMT endows cells with stem cell characteristics, Mani et al. proposed that if the EMT provides normal epithelial cells with stem cell characteristics, perhaps it also provides carcinoma cells with these traits [22]. The authors demonstrated that in limiting dilutions, transformed mammary epithelial cells with ectopic expression of the EMT factors Snail or Twist formed more tumors than cells that had not undergone an EMT [22]. Since this report, it has been demonstrated that the EMT promotes cancer stem cell characteristics in various cancers, including pancreatic [123], colon [124], hepatocellular [125], lung [126,127], prostate [128], and head and neck [129].

While there are quite a few studies about putative ovarian CSCs and their characteristics, less is known about their relationship with the EMT in ovarian cancer. There are a few pieces of evidence to support that the EMT may actively contribute to the CSC phenotype. The EMT-inhibiting miRNA-200 has been shown to reduce the tumorigenicity of a population of putative ovarian CSC [130]. Additionally, CD24-expressing ovarian CSCs are more invasive and express higher levels of EMT-associated genes than CD24-negative cells [131]. The field is currently lacking well-designed studies that experimentally induce an EMT and thoroughly assess tumorigenicity and other CSC traits; however, there is no evidence to suggest that ovarian cancer is different than the other epithelial cancers where the EMT has been implicated in promoting CSC characteristics.

**Immunosuppression**

Immune cell evasion is a hallmark characteristic of cancer: while various immune cells infiltrate the tumor microenvironment; they fail to launch effective attacks against the cancer [132]. The presence of immune cells within ovarian tumors is well-documented; however, the antitumor response is often negated by strong immunosuppressive signals [133,134]. These signals are also often associated with a worse prognosis for the patient. For example, patients with high intratumoral levels of FOXP3, a marker of immunosuppressive regulatory T-cells, have a dramatically reduced survival compared to those with low levels [135]. This immunosuppressive program is the net result of complex interactions between the immune system, the tumor cells themselves, and adjacent noncancer tissue.

There is a strong relationship between immune cell regulation and the EMT. In fact, many of the EMT-inducing cytokines also serve as immunoregulators, including members of the TGFB family, various interleukins, and more. While there is a fair amount of work documenting the cooccurrence of the mesenchymal state and immunosuppressive environments in various cancers, more work is required to improve our understanding of how these phenomena arise and how they are maintained [136]. It is currently unclear to what extent the EMT promotes immunosuppression, how much the EMT is driven by cytokines secreted from immunosuppressive immune cells, or how additional factors such as stromal cells and vasculature contribute to both. It is likely the net effect of signals from many sources, including both the immune and cancer cells.

The relationship between EMT and immunosuppression has yet to be studied in ovarian cancer; however, findings from other carcinomas may provide insight into its relevance. Various cytokines released from tumor-infiltrating leukocytes have been shown to promote EMT and metastasis [137], suggesting that the immune component contributes to carcinoma cell plasticity. Interestingly, the carcinoma cells themselves can also promote immunosuppression. When cocultured with splenocytes, both murine and human melanoma cells overexpressing the EMT-inducing transcription factor Snail cause, compared to control melanoma cells, reduced leukocyte proliferation, a lower proportion of CD4+ and CD8+ T-cells, and enhanced differentiation of immunosuppressive regulatory T cells and dendritic cells [138]. Additionally, inhibiting Snail with an intratumoral injection of small-interfering RNAs abrogated immunosuppression, leading to an enhanced infiltration of CD4+ and CD8+ T-cells and impaired tumor growth [138].

The mechanisms promoting the immunosuppressive phenotype are less clear; however, most findings point to the secretion of immunosuppressive cytokines. In a lung adenocarcinoma model, tumor cell secretion of TGFB has been shown to skew tumor-associated macrophages toward an anti-inflammatory “M2” phenotype by inhibiting TNF signaling through the interleukin receptor-associated kinase (IRAK)-M [139]. Another study has shown that miR-200 and Zeb1 regulate programmed death-ligand 1 (PD-L1) expression in lung cancer cells, with the mesenchymal state being associated with elevated PD-L1 secretion, causing suppression of CD8+ T-cells, which could be alleviated by treatment with an anti-PD-L1 antibody [140]. A recent study using breast carcinoma xenograft models has demonstrated that injecting flow cytometry-enriched EPCAMlo (mesenchymal) cells lead to immunosuppressive tumors relative to EPCAMhi (epithelial) cells [141]. Also, injecting various mixtures of these epithelial and mesenchymal cells results in comparable immunosuppressive phenotypes, suggesting that even a relatively small population of mesenchymal cells [~10%] can program the majority of the tumor.
microenvironment, protecting the epithelial component from the antitumor response [141] (Fig. 3).

**A THERAPEUTIC OUTLOOK: TARGETING PLASTICITY**

Given the collection of procancer traits regulated by the EMT, therapeutic control over carcinoma cell plasticity may yield tremendous benefits. Indeed, many have discussed developing therapies tailored to the molecular subtype of a given cancer [20,70,71]; however, discussion has focused on choosing therapies based on sensitivities of subtypes, rather than attempting to reprogram the cancer itself. Targeting the sensitivities of subtypes would likely improve outcomes over conventional therapy; however, given the heterogeneity within tumors, it seems probable that not all cells would be equally sensitive, leading to tumor recurrence. A therapy based on reprogramming the more-mesenchymal carcinoma cells to an epithelial state could render the tumor less metastatic and more susceptible to platinum-based chemotherapy. It may also activate the immune system, promoting an antitumor response, as was observed in the above-mentioned study that found an intratumoral injection of small-interfering RNAs against Snail lead to immune activation within the tumor [138]. Ultimately, therapeutic reprogramming may be an effective complement to other treatments.

**Does Plasticity Actually Play a Role in Tumor Progression?**

Plasticity, by its strictest definition, is difficult to observe in the context of cancer, as it requires the tracking of an individual cell’s phenotype over time. Often, we can only interrogate tumors by collecting molecular and visual data as snapshots of the moment the sample was collected. Temporal information is rarely acquired. Occasionally, it is possible to collect repeated samples from a tumor—before and after a chemotherapy regimen, for example—but plasticity is always confounded with compositional differences, such as the enrichment of a population of chemoresistant cells, that were present, but proportionally rare before treatment. It is clear that ovarian cancer cells display plasticity when experimentally forced to do so, but then again, skin cells can be reprogrammed into pluripotent stem cells with the right experiment. So the question remains, do ovarian carcinomas display plasticity in their natural setting?

Given the number of signaling pathways that seem to regulate the EMT, it seems reasonable to assume that the cancer cells do respond to changes in the tumor microenvironment, which likely alter the milieu of signaling ligands. The above-mentioned study [110] that described an induction of an EMT gene expression signature when ovarian cancer cells were transferred from adherent to suspension cultures is promising because it did not involve ectopically expressing EMT genes and demonstrated that these cells can dynamically respond to their environment. Moving forward, genetic lineage tracing experiments to permanently label cells upon the induction of an EMT, followed by functional selection such as metastasis or chemotherapy treatment of tumor models will greatly improve our understanding of plasticity in the context of tumor progression. Until then, while we know ovarian carcinoma cells are capable of remarkable plasticity, the assumption that plasticity plays a role in tumor progression is strictly hypothetical.

**CONCLUSION**

Cell plasticity is critical for many biological processes, from embryo development and tissue homeostasis to cancer. Following each ovulation, the OSE relies on its plasticity to undergo an EMT and repair the ovulatory wound. Likewise, the FTE relies on this plasticity to...
maintain homeostasis. This same plasticity is thought to contribute to some of the most detrimental features of ovarian cancer, including metastasis and the resistance to chemotherapy. Improving our understanding of the molecular determinants of this phenomenon would provide valuable insight into ovarian homeostasis and could potentially improve personalized medicine: new subtypes of ovarian cancer could be defined, targeted therapies for each subtype could be developed, and perhaps plasticity itself could be targeted, steering a cancer to a more-manageable state.

Discussion of epithelial cell plasticity often revolves around the notion of a cell that is capable of transition between epithelial and mesenchymal states, as it has been described in this chapter. This focus is likely the consequence of the transition being readily observable and resulting in remarkable functional changes. However, it should be recognized that cellular plasticity is not limited to this transition and likely comprises responses to many transient stimuli, such as inflammation, hypoxia, circadian rhythm, and more. Environmental changes throughout the reproductive cycle beyond ovulatory wound repair may also drive transient responses in the OSE and FTE that may be of interest for understanding ovarian homeostasis and tumorigenesis. As technology improves and methodologies are developed to assess broadly cell state in vivo, it will become increasingly possible to determine the effect of these natural stimuli on the OSE, FTE, and other tissues of the ovary. Only then will we be able to grasp fully the complexities of this dynamic organ.

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33. PHENOTYPIC PLASTICITY AND THE ORIGINS AND PROGRESSION OF OVARIAN CANCER


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