Metastatic growth is a pivotal, often lethal step in cancer progression in which cancer cells leave the primary tumor to travel to distal sites where they form new (i.e., secondary) tumors (Langley and Fidler, 2011). While the shedding of cancer cells from primary tumors is common, the formation of secondary tumors at distant sites is, fortunately for the patient, usually highly inefficient. Only <0.01% of circulating cancer cells successfully establish secondary growth (Fidler, 1970). This lack of success is likely due to anoikis (literally meaning “without home”) that occurs when cancer cells leave the tissue microenvironment, also called tumor stroma (literally meaning “bed”), provided by the primary tumor. Loss of stroma means loss of attachment of the cancer cells to the extracellular matrix (ECM) in the stromal tumor microenvironment.

Loss of attachment deprives the cancer cells of essential growth and survival signals. Therefore, isolated cancer cells are often much less tumorigenic than those embedded in stroma, and immune destruction of cancer stroma substantially reduces the success of cancer cells to implant and cause tumors (Singh et al., 1992).

As a prominent exception to this rule, high-grade serous ovarian cancer (HGSOC) has found an efficient way to overcome this fundamental hurdle. For reasons that had remained mostly obscure, cancer cells leaving the primary ovarian tumor establish metastases highly successfully in the abdominal or pleural cavities. This property makes HGSOC the most lethal female malignancy. In this issue of JEM, Gao et al. (https://doi.org/10.1084/jem.20180765) demystify the exceptional metastatic success of ovarian cancer, the most lethal female malignancy: fibroblasts form heterotypic aggregates with disseminating cancer cells, thereby providing them with reciprocal signaling and matrix for adherence.

Hans Schreiber

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Fibroblasts: Dangerous travel companions

Schreiber
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mor-associated macrophages (TAMs), are
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also correlated with poorer survival in various,
including ovarian, cancers. By contrast, elimi-
nation of neutrophils inhibits tumor growth (Pekarek et al., 1995) and macrophage rec-
uitment into the peritoneal cavity (see ref-
ences in Pekarek et al., 1995).

The realization that tumor-associated
fibroblasts play a decisive role in the ag-
gressiveness of ovarian cancer calls for a re-
evaluation of realistic possibilities to target
the stroma of cancers specifically and effect-
ively. The authors used the Abelson-kinase
inhibitor imatinib to inhibit CAFs or lipo-
some clodronate to destroy TAMs. However,
both drugs are toxic and inhibited meta-
static spread only transiently. Already two
generations ago, outstanding immunologists
showed that the most effective targets for
cancer rejection were the so-called unique
tumor-specific rejection antigens recognized by
T cells. In 1995, these unique antigens were
shown to be caused by nonsynonymous sin-
gle nucleotide variants (nsSNVs) and shown to
be effective targets for mutation-specific
adoptive T cell transfer (Monach et al., 1995).
These nsSNVs are now also simply referred to as mutant neoantigens, and it appears that
these random, mutant, truly cancer-specific antigens represent the relevant targets of
most successful human immunotherapies (see references in Deniger et al., 2018).
HGSOC has an average of 46 nsSNVs; if only
half of them were expressed at sufficient
levels, the set of usually 12 different anti-
gen-presenting HLA molecules could create
>250 cancer-specific targets. At least some
of these nsSNVs will be cross-presented by
BM-derived as well as non–BM-derived stro-
mal cells, both of which must be targeted to
prevent cancer escape in experimental mod-
els (Zhang et al., 2007). HGSOC diagnosed
with ascites is presently almost invariably
lethal, but most of these patients can be ef-
ectively treated by chemotherapy, which re-
sults in a relapse-free interval often lasting
>1 yr. Thus HGSOC is an ideal starting point
for mutation-specific T cell therapy because
this interval could be used to generate a set
of autologous T cell receptors for specifically
targeting the patient’s neoantigens. Indeed,
recent results showed that autologous, truly
cancer-specific T cells to mutant antigens
could be induced in five of seven HGSOC pa-
ents and that responses are not limited by a
relatively low mutational burden (Deniger et al., 2018). Such autologous TCRs transduced
into autologous peripheral T cells and adop-
tively transferred into the patient during re-
mission may well prevent relapse of HGSOC
and would represent a truly personalized,
truly cancer-specific therapy. The research
by Gao et al. (2019) is an important guide to
focus on those mutant neoantigens that are

Heterotypic aggregates are responsible for the unusual metastatic success of HGSOC, the most lethal fe-
male malignancy. When the tumor cells leave the primary ovarian cancer to enter the abdominal cavity,
they do not travel alone. Instead, they rapidly form small aggregates by surrounding an inner tissue core of
fibroblasts, macrophages, and ECM. This inner core provides the HGSOC cells with attachment and reciproc
signals to escape death by anoikis. The signals also help the aggregates attaching to mesothelium-cov-
ered surfaces and establish metastatic growth. Neutrophils are essential in the recruitment of progenitors
of macrophages from the BM and in the recruitment of fibroblasts from local perivascular reservoirs. All
HGSOCs harbor numerous patient-specific mutations that may be recognized by T cells as cross-presented
antigens on fibroblasts and/or macrophages in tumor stroma. This would provide a truly cancer-specific,
truly personalized approach to stromal targeting in cancer therapy.

rectional signaling loop: epidermal growth
factor receptor (EGFR)–positive cancer cells
release TGFβ1 that activates fibroblasts to
produce ECM components for the cancer cells to receive pro-survival
signals, mobilize energy sources, and ex-
press ITGAS needed for attachment (Curtis et al., 2018). However, the metastatic suc-
cess of HGSOC probably also depends on
the up-regulation of additional genes. Thus,>700 genes were overexpressed in HGSOC
ascites cells when compared to primary as
well as metastatic HGSOC cancer cells, and
these genes were involved in multiple bi-
ological processes. By contrast, <20 genes
were overexpressed in LGSOC ascites cells
when compared to primary as well as metas-
static LGSOC cancer cell samples.

The activation state of cancer-associated
fibroblasts (CAFs) generally correlates with
the aggressiveness of cancers (see references in
Arina et al., 2016), and CAFs increase the
proliferation, metastasis, and chemoresis-
tance of ovarian cancer (Wang et al., 2016;
Curtis et al., 2018). Interestingly, the other
major component of cancer stroma, tu-
mor-associated macrophages (TAMs), are
also found in the center of the heterotypic
spheroids in the ascites of HGSOC patients (Yin et al., 2016). TAMs also participate in
the bidirectional EGF/EGFR signaling axis. Surprisingly, the sources of the major com-
ponents of cancer stroma have only been
cursively identified rather recently through experiments using parabiotic and chimeric mice. TAMs come from the bone
marrow (BM), whereas tumor endothelial
cells and CAFs come from local sessile stem
cell reservoirs (see references in Arina et al., 2016). These mesenchymal stem cell res-
erves are of perivascular origin and are
found in every organ, even though fibro-
blasts obtained from different anatomical
sites differ (see references in Arina et al., 2016). It remains unclear how fibroblasts
exit the ovarian primary tumor as envi-
sioned by Gao et al. (2019) and whether the
fibroblasts also come from stem cell sources
at other sites. The latter is consistent with
the finding that intraperitoneal injection of
spontaneous murine HGSOC cells induced
such heterotypic spheroids.

Peyton Rous already found that the suc-
cess of a tumor implant depends directly on
whether it elicits a vascularizing stroma
reaction (Rous, 1910). Thus, the spheroids
must vascularize after adhering to mesothe-
lial surfaces, and the initiating critical cell is
likely the neutrophil. Neutrophils produce
tissue inhibitor of metalloproteases (TIMP)–
free matrix metalloproteinase-9 and neutro-
phil elastase to degrade SDF-1 that normally
locks CXCR4-positive stromal mesenchy-
mal, hematopoietic, and angiopoietic pro-
genitors at their sites of origin (Petit et al., 2002). High neutrophil–lymphocyte ratios
 correlate with poorer survival in various,
including ovarian, cancers. By contrast, elimi-
nation of neutrophils inhibits tumor growth (Pekarek et al., 1995) and macrophage rec-
uitment into the peritoneal cavity (see ref-
ences in Pekarek et al., 1995).
highly expressed to become effective cancer-specific targets, not only for the cancer cell but also for the tumor stroma.

Acknowledgments

H. Schreiber is supported by National Institutes of Health grants R01-CA22677 and R01-CA37156.

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