Editorial

Dickkopf-1 helps metastasis by immune evasion

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Cancer metastasis still remains leading cause of cancer-related death. To diminish the rate of cancer-related death, the critical issue is to deal with recurrences and chemo-resistance. Metastasis consists with sequential steps; tumor invasion, intravasation, extravasation and colonization in second organs. Accumulating evidence suggests that a cell population with stem cell-like tumor cells exists as dormant in the body. Once awaken from dormancy, the cells start growing. So far, it has been reported that dormant tumor cells are involved in metastasis (1,2). Does only a small population carry over the phenotype? How can dormant cells survive during tumor progression?

Recently, Malladi *et al.* clearly provide evidence that a cell population with stem cell-like phenotypes plays a critical role in metastasis by escaping from natural killer cell-mediated surveillance (3). The authors firstly isolated so-called "latent competent cancer (LCC) cells" from distant metastatic lesions upon relapse long time (3 months) after intracardiac tumor cells injection. This study more focused at a colonization step during tumor progression after extravasation. Their experimental protocol successfully enriched cell populations with stem or progenitor type. Consistently, these cells highly expressed SOX2/SOX9, master genes among stem cell-like signature (SOX2 for lung cancer; SOX9 for breast cancer). SOX expression was detected at single disseminated LCC cells but rarely in proliferating cell clusters, emphasizing that LCC cells carry phenotypically stem cell-like signature, compared to their parental counterparts. As LCC cells of a breast cancer model, $CD44^{high}/CD24^{low}$ mammary cell populations were enriched for SOX9, which is consistently a major population of cancer stem cells (CSCs) in breast cancer.

This raises fundamental questions of whether or not acquisition of LCC properties is cell-autonomous, and whether LCC-hosting metastatic niche is pre-formed as tissue stem cell niche or post-formed after parental LCC arrival. Defining cell populations of LCC out of usual cell cultures may answer the first question. However, experiments with *in vitro*-isolated $CD90^{+}$ $CD24^{+}$ CSCs (4) may not explain LCC features. Their procedure to establish LCC cells from lungs does not require primary tumor establishment, and therefore LCC metastatic niche is not what we call pre-metastatic niche (5). Lung tissue stem cell niche is poorly defined (6), but still could be pre-formed LCC niche. Irrespective of the time point of parental LCC arrival, LCC cells are stimulated by the surrounding microenvironment. For example, overgrowth of EphB3-overexpressing colon adenoma cells driven by activated adenomatous polyposis coli (APC) mutation-mediated Wnt signaling is inhibited by binding of EphB3 to its ligand ephrin-B1 in normal epithelial cells (7). The opposing gradient hypothesis between Eph and ephrin in breast cancer cells and glioblastoma cells has been documented (8-10). EphA2/ephrin-A1 expression level ratios are high in those CSCs. Progenitor cells have an opposite expression pattern.

Malladi *et al.* also showed that natural killer (NK) cell-mediated cytotoxicity was abrogated in LCC cells. Mechanistically, the expression level of CD155, a ligand for the cancer cell killing receptor CD226, was down-regulated. By using *in vitro* NK-mediated cytotoxicity assay, quiescent LCC cells showed resistance to cytolysis when incubated with NK cells. Furthermore, the signaling pathway classifier analysis of LCC cells in quiescent state showed that Myc, Wnt, and NF-κB signaling were markedly reduced.

Dickkopf-1 (DKK1) is a secreted molecule that has been

known as a Wnt inhibitor, and overexpressed in various cancers. DKK1 is also suggested to be a novel prognostic biomarker for lung and esophageal carcinomas (11). By using PrognoScan database (http://www.abren.net/PrognoScan/), Smith's study in colorectal cancer indicates that higher expression of DKK1 is associated with poor prognosis. Malladi *et al.* showed that the LCC cells obtained from human breast cancer cells or lung adenocarcinomas express relatively higher expression of DKK1 than the parental cells. Intriguingly, the knockdown of SOX2 in lung LCC cells dramatically reduced DKK1 expression, indicating that DKK1 is at least partly regulated by SOX2.

As emphasized again, the metastatic steps described by Malladi *et al.* are from extravasation to colonization. More recently, D'Amico *et al.* showed that DKK1 regulates myeloid derived suppressor cells (12). In tumor microenvironment, a bunch of variety of immune cells (i.e., inflammatory monocytes, macrophages, T/B cells, etc.) play a role in tumor cells-immune cells interaction (13,14). In addition, several reports suggest that macrophages induce Wnt ligand upon stimulation (15,16). Thus, DKK1 may be widely engaged in immune-microenvironment during tumor progression.

So far, premetastatic niche becomes a new therapeutic target against metastasis. The premetastatic niche is defined as supportive and favorable microenvironment for tumors in second organs. As mentioned above, the study by Malladi *et al.* indicates that DKK1 in LCC cells contributes to, at least in part, the colonization step of metastasis by protection against NK cell-mediated immune attack.

The premetastatic soil is an inflammatory microenvironment in the absence of tumor cells and established by the remote control of distantly-located primary tumor cells. The metastatic microenvironment that hosts LCC cells is post-formed since the LCC cells by themselves are tumor cells. However, if we take LCC cells in quiescence as absence of growing tumor cells, the LCC microenvironment could be assumed to be premetastatic in the sense that metastatic tumor cells manifest themselves on the spot from the LCC cells but not from the primary site.

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