SPSB1 May Have MET Its Match during Breast Cancer Recurrence

Yuanbo Qin and Sandra S. McAllister

Summary: Disease recurrence is the most common cause of death for patients with breast cancer, yet little is known about the molecular mechanisms underlying this process. Using inducible transgenic mouse model systems, Feng and colleagues identified SPSB1 as a determinant of breast cancer recurrence by virtue of its ability to protect tumor cells from apoptosis through c-MET activation. Cancer Discov; 4(7); 760–1. © 2014 AACR.

See related article by Feng et al., p. 790 (2).

Breast cancer is a heterogeneous disease that is clinically defined by the expression of estrogen (ER) and progesterone (PR) hormone receptors as well as the HER2 cell-surface receptor. These underlying histopathologic features have been useful in determining a patient’s recommended therapy. For example, drugs targeting the estrogen signaling pathway are used for women with ER-positive breast cancer. Similarly, women with HER2-positive breast cancers are currently treated with anti-HER2 therapies, which have shown significant clinical benefit. Despite the initial success of targeted therapies, approximately 20% of patients with breast cancer develop recurrent disease, which is thought to represent resistance to a given targeted therapy. As such, a better understanding of the biologic processes that drive recurrent disease is essential.

To address the challenges that recurrent breast cancers present, Gunther and colleagues (1) have developed bi-transgenic mouse models that enable them to regulate oncogene expression in the mammary gland using a doxycycline-responsive gene expression system. Treating these mice with doxycycline turns “on” oncogenes that are involved in mammary tumor development and leads to the formation of primary mammary tumors. Subsequently, switching those genes “off” by doxycycline withdrawal after tumors have formed causes most of the tumors to essentially disappear, ostensibly via apoptosis due to withdrawal of the oncogene—a process that has been termed oncogene addiction. These models are thus meant to mimic the treatment of primary human breast cancers with targeted therapies. However, as is apparent from clinical experience with targeted therapies, some of the tumors that originally regressed in the mice will rebound, and these mice will develop recurrent disease following a variable latency period after doxycycline withdrawal.

In the current issue of Cancer Discovery, Feng and colleagues (2) used such mouse models to modulate the expression of HER2, c-MYC, or WNT-1 oncogenic signaling. By comparing paired primary and recurrent mammary tumors, they found that both mRNA and protein levels of the SPRY domain-containing SOCS Box protein 1 (SPSB1) were significantly elevated in tumors that relapsed after oncogene withdrawal in all three transgenic mouse models. SPSB1 belongs to the SPSB protein family, which consists of four members (SPSB1–4). Although some of the SPSB proteins function as adaptors for ubiquitin ligases to regulate protein degradation (3), the function of SPSB1 in breast cancer had not been fully investigated.

While focusing on the inducible HER2 transgenic mouse model, Feng and colleagues (2) learned that SPSB1 was both necessary and sufficient for tumor recurrence by performing experiments in which they orthotopically injected mammary tumor cells that either overexpressed SPSB1 or expressed sh-hairpin RNA to suppress SPSB1 expression. Interestingly, the SPSB1-overexpressing cells were at a selective disadvantage in the tumors that formed during the period in which HER2 was expressed; however, these cells preferentially survived and were expanded within the recurrent tumors that formed after HER2 withdrawal. Because proliferation rate differences between control and SPSB1-overexpressing cells did not explain the selection for the latter population, the authors asked whether SPSB1-expressing cells were resistant to oncogene withdrawal-induced apoptosis. In contrast to control cells, the apoptotic rate of the SPSB1-expressing tumor cells remained low, even after oncogene withdrawal, suggesting that SPSB1 protects cells from apoptosis upon oncogene deprivation. It is noteworthy that the expression of SPSB1 also provided a survival advantage to both HER2-negative and triple-negative (ER/PR/HER2-) human breast cancer cells that were treated in vitro with chemotherapeutic agents, suggesting that SPSB1-mediated survival might constitute a general mechanism of therapeutic resistance.

Previous studies have demonstrated that SPSB1 can bind to the cell-surface receptor c-MET to enhance the hepatocyte growth factor (HGF)-induced ERK–ELK-1–serum response element pathway (4). c-MET is a receptor tyrosine kinase that is predominantly expressed by epithelial and endothelial cells. Activation of the c-MET receptor by its ligand, HGF, promotes receptor tyrosine phosphorylation, thereby triggering the
recruitment of signaling protein complexes required for activation of the RAS-ERK–MAPK, RAC1–CDC42–PAK, GAB1–PI3K–AKT, and JAK–STAT pathways (5). Results from other studies of various malignancies have shown that HGF–c-MET signaling prevents apoptosis through either the PI3K–AKT or JAK–STAT pathways (5). These findings, in part, prompted the authors to test whether the ant apoptotic effects of SPSB1 are mediated by c-MET. Hence, by performing coimmunoprecipitation assays with the inducible HER2 cell lines, the authors consistently found that SPSB1 bound to c-MET irrespective of HER2 expression. Nevertheless, c-MET activation occurred only after HER2 deinduction and relied on SPSB1 expression. Similarly, c-MET was required for SPSB1-mediated tumor cell survival in response to acute HER2 downregulation.

In light of the observations described above, the authors interrogated the publicly available human breast cancer gene expression datasets for which clinical outcome was available. They specifically examined the relationship between SPSB1 expression and relapse-free survival. Consistent with their findings in mice, elevated SPSB1 expression in primary tumor tissues correlated with decreased recurrence-free survival and served as an independent prognostic factor for breast cancer recurrence. When examining the association between SPSB1 expression and breast cancer subtype, they found that SPSB1 expression correlated with HER2-positive, ER-negative, and PR-negative breast cancers, as well as basal-like breast cancer, a particularly aggressive form of the disease for which there are no targeted therapies available.

The fact that SPSB1 potentiated c-MET signaling provides a compelling argument that association between SPSB1 expression and relapse-free survival is at least partially dependent on c-MET pathway activity. In fact, several lines of evidence have suggested that dysregulated c-MET signaling may contribute to breast cancer recurrence: overexpression of c-MET has been observed in 20% to 30% of invasive breast cancers, c-MET expression has been independently associated with basal-like breast cancer, and there is a statistically significant correlation between c-MET expression and poor prognosis (6). By performing meta-analysis of the datasets after adjusting for c-MET signaling activity, Feng and colleagues (2) no longer obtained a statistically significant association between SPSB1 and relapse-free survival. This observation strengthened the notion that SPSB1 is biologically relevant in the context of c-MET signaling and that targeting the c-MET pathway might provide an effective strategy for breast tumors that display elevated SPSB1 expression.

Recent work has demonstrated that c-MET activation by stromal-derived HGF is responsible for conferring drug resistance in BRAF-mutant melanomas treated with RAF inhibitors (7). Similarly, resistance to EGFR inhibitors occurred as a consequence of c-MET overexpression in non–small cell lung cancers (8). The work by Feng and colleagues (2) provides another possible molecular mechanism for the development of c-MET-mediated drug resistance: upregulation of a binding partner that potentiates c-MET activity. Hence, identifying such regulators of c-MET signaling has the potential to reveal novel therapeutic targets.

The findings reported by Feng and colleagues (2) have the potential to enhance our understanding of the mechanisms underlying breast cancer recurrence. As with most good studies, additional questions are now raised that should lead to further exploration. For example, it is not yet clear how SPSB1 regulates c-MET activation, and elucidating this mechanism may provide new insights into oncogenic regulation of the c-MET signaling pathway in the context of breast cancer relapse. In addition, earlier work from the same group revealed that downregulation of the tumor suppressor prostate apoptosis response-4 (PAR-4) is critical for evading apoptosis during breast cancer recurrence in their doxycycline-inducible HER2/neu, c-MET, and Wnt-1 mouse models (9). Interestingly, another study had shown that human PAR-4 protein harbors a recognition site for SPSB1 (10). Nevertheless, the authors could not detect interaction between murine PAR-4 and SPSB1, as the homologous SPSB1 recognition site is not present in the murine PAR-4 protein (2). It therefore remains to be tested whether PAR-4 intersects with the SPSB1–c-MET pathway during breast cancer recurrence. In this same light, it is also likely that there are multiple ways to avoid apoptosis during therapeutic resistance. Hence, a more global understanding of the involvement of other signaling networks using similar mouse models stands to be informative, making this a promising area of future research.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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REFERENCES

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