Small cell lung cancer (SCLC) represents 13% of all newly diagnosed cases of cancer worldwide, or more than 180,000 cases per year. In contrast with non–small cell lung cancer (NSCLC), it is not associated with specific somatic mutations (1). The prognosis for patients with SCLC has not improved and treatment has remained substantially the same for the last 25 years. The first-line treatment of choice in extensive-stage SCLC is 4 to 6 cycles of etoposide combined with cisplatin or carboplatin, with a median survival of 8 to 13 months, and a 2-year survival rate of 5%. For patients with limited-stage disease, the standard treatment is the same chemotherapy regimen with the addition of thoracic radiotherapy, and median survival is 15 to 20 months, with a 2-year survival rate of 20% to 40% (1). The loss of p130 accelerates the development of data indicate that of 20% to 40% (1). The median survival is 15 to 20 months, with a 2-year survival rate of 5%.

Commentary on Byers et al., p. 798 (3).

IN THE SPOTLIGHT

A Genetic Snapshot of Small Cell Lung Cancer
Rafael Rosell1,2 and Luciano Wannesson3

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by colony formation of A549 NSCLC cells decreased under hypoxic conditions when treated with PARP inhibitors (4). As the authors suggest (3), clinical trials with PARP inhibitors are warranted in SCLC. However, when predicting the efficacy of PARP inhibitors, we should consider not only PARP1 expression but also the potential loss of p130, which could abrogate the effect of PARP inhibition on BRCA1 and RAD51.

Resistance to PARP inhibitors may be related to the loss of 53BP1, as occurs in triple-negative, BRCA1-mutated breast cancer. BRCA1 displaces 53BP1 from double-strand breaks, enabling resection at the break site by factors such as CtIP, which promotes RPA loading onto single-stranded regions of DNA. RPA is displaced by RAD51, leading to error-free template-directed repair of the double-strand break. However, in cells with loss of BRCA1, 53BP1 is not displaced, and DNA repair is abrogated (5). Because the authors found that 53BP1 was overexpressed in the SCLC lines (3), we can speculate that the high sensitivity to PARP inhibitors in the SCLC cell lines may be due in part to the effect of the 53BP1 expression.

In response to DNA double-strand breaks caused by cisplatin chemotherapy, MDC1 binds to γH2AX and controls the formation of damage-induced 53BP1 and BRCA1 foci, in part by promoting efficient H2AX phosphorylation. Other proteins, such as MCPH1, bind to BRCA2 and regulate the localization of BRCA2 and RAD51 at sites of DNA damage (Fig. 1). BRCA1 was identified as a differential modulator of chemotherapy response (5), and the decrease in the expression of BRCA1 and RAD51 induced by chronic hypoxia could offset chemoresistance and increase sensitivity to cisplatin, although not to paclitaxel (6). Therefore, several lines of evidence indicate that PARP inhibitors can be synergistic with cisplatin-plus-etoposide in SCLC.

In a subgroup of triple-negative breast cancers, RB and TP53 were inactivated, with some genetic traits that are similar to those identified in SCLC. In triple-negative breast cancers, overexpression of FGFR2 has been observed (5), as has also been described in SCLC (7), making FGFR2 a potential target for treatment.

Intriguingly, the results of the Heymach group are similar to those regarding the SV40 T/t antigen intrinsic 120-gene signature, in which 85 of the genes are closely related to p53, pRB, and E2F genetic networks and in which EZH2 was also upregulated (8). Heymach’s group has identified the overexpression of EZH2 in SCLC, indicating that it could be an important target for treatment. EZH2 is a histone modifier protein that functions as a methyltransferase at lysine 27 of histone H3. EZH2 is also a member of the polycomb group of proteins and belongs to polycomb repressive complex 2.

Figure 1. A, Signaling pathways depicting the position of BRCA1, RAD51, and 53BP1 in homologous recombination. B, The role of EZH2 and its relationship with BRCA1 in breast cancer is also illustrated. Other signaling components in triple-negative breast cancers are also shown. Green, tumor suppressors upstream of the homologous recombination pathway; blue, tumor suppressors downstream of the homologous recombination pathway; purple, oncogenes; yellow, tumor suppressors. BC, breast cancer; P, phosphorylation; PARPi, inhibitor; SU, sumoylation; TNBC, triple-negative breast cancer; Ub, ubiquitination. For further explanation, see ref. 5. (Figure reproduced, with permission, from ref. 5.)
Overexpression of EZH2 has been associated with poor outcome in prostate and breast cancers. EZH2 negatively regulates the expression of DAB2IP, which is a unique scaffolding protein that regulates several signaling pathways, including apoptosis signal-regulating kinase 1 (ASK1). ASK1 can activate several proapoptotic proteins, including BIM (9). High EZH2 protein levels have been associated with upregulated expression of AKT and decreased nuclear expression of phospho-EZH2 protein levels have been associated with upregulated vate several proapoptotic proteins, including BIM (9). High apoptosis signal-regulating kinase 1 (ASK1). ASK1 can acti- rates the expression of DAB2IP, which is a unique scaffolding pro- tein (MAP)/extracellular signal-regulated kinase (ERK) kinase (MEK) inhibitors. In breast cancer, the activation of the MEK/ ERK1/2/ELK-1 pathway leads to EZH2 overexpression (ref. 12; Fig. 1). What is not known is if overexpression of EZH2 in SCLC also downregulates BRCA1 and if the elevated levels of EZH2 could be a consequence of the activation of the MEK/ ERK1/2/ELK-1 pathway. In this case, the high expression of EZH2 could be druggable with MEK inhibitors.

The fundamental findings of the authors can lead to further insight into SCLC. For example, loss of miR-26a has been related to increased expression of EZH2 and AEG-1 (also known as MTDH), which confers chemoresistance (13). The identification of elevated expression of PARP1 in SCLC paves the way for introducing novel effective targeted therapies that can lead to definite progress in the treatment of this disease, in which trials with BCL2 inhibitors currently are being conducted (7).

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No potential conflicts of interest were disclosed.

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