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Editorial

EDITORIAL

Everything Old is Neu Again: Cellular Senescence in HER2-Positive Breast Cancer

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An irreversible cell proliferation arrest, senescence can be triggered by a variety of stressors, including oncogenes. In oncogene-induced senescence (OIS), senescent cells are capable of releasing a wealth of factors, collectively termed senescence-associated secretory phenotype (1,2). In addition to including components necessary to establish and maintain the senescence program, the secretome not infrequently includes protumorigenic factors, which have been proposed to contribute to tumor progression in a cell nonautonomous manner (1–3).

In this issue of the Journal, Zacarias-Fluc and colleagues at the Vall d'Hebron Institute of Oncology in Barcelona look at a previously unstudied aspect of the biology of human epidermal growth factor receptor 2 (HER2)–positive breast cancer, namely the role played by cellular senescence in the disease (4). Their study is interesting for the new light shed on the disease and potentially provocative with regard to both the prognosis and treatment of the disease.

In brief, the authors demonstrate that HER2 amplification in breast cancer is associated with oncogene-induced senescence, a previously described tumor suppressor mechanism with several known oncogenes. Though tumor cell senescence might seem a pleasant outcome, there is an important catch: the senescent cancer cells display a distinct secretome characterized by secretion of Il-6. And the secretion of Il-6 by these senescent tumor cells is most definitely not a good thing.

IL6 has been extensively studied in preclinical models of breast cancer. Its effects are protean. As demonstrated by previous work, IL-6 mediates HER2-driven growth via activation of the JAK-STAT pathway (5), and inhibition of IL-6—at least in some models—inhibits tumor growth, as shown in patient-derived xenografts in the current paper. Interestingly, work by others has suggested that senescent mesenchymal cells can perform the same function, promoting proliferation and migration of breast cancer cells (6). In addition, IL-6 can induce trastuzumab resistance via STAT3 hyperactivation, which in turn increases tumor cell production of MUC1 and MUC4 (7) and via expansion of the cancer stem cell population (8). Il-6 is also a well-described promoter of angiogenesis, invasion, and metastasis.

How important is this novel mechanism in the clinic? This question is not easily addressed. Quantitative measurement of senescent cells in clinical tumor samples is not straightforward. Circulating IL-6 has been measured in several studies of human breast cancer patients, with elevated levels generally being associated with impaired prognosis (reviewed in [8]), but such measurements may not reflect either tumor cell senescence or, for that matter, what is going on inside the tumor. Similarly, intratumoral measures of IL-6 have given conflicting results as regards prognosis (9).

The IL-6 story has another potential implication, currently unexplored but certainly worthy of explanation. If HER2-related senescence results in IL-6 production, with all of its downstream effects on invasion, metastasis, growth, and drug resistance, then could interruption of IL-6 represent a therapeutic target in HER2-positive breast cancer?

This question is interesting in part because IL-6 has recently become a therapeutic target in multicentric Castleman's Disease, a rare lymphoproliferative syndrome driven by IL-6 (10). Recently the US Food and Drug Administration approved siltuximab (a chimeric monoclonal antibody against interleukin) based on a randomized, placebo-controlled trial demonstrating durable tumor and symptomatic responses. Could this agent, combined with HER2-targeted therapy, have a beneficial effect in HER2-positive breast cancer resistant to standard therapies? The HER2 space is a crowded one in breast cancer, but the approach seems reasonable to test, at least in appropriate preclinical models.

Note

The authors have no conflicts of interest to declare.

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