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Interleukin-6 induces increased motility, cell-cell and cell-substrate dyshesion and epithelial to mesenchymal transformation (EMT) in breast cancer cells

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Dear Editor --

Two recent articles in ONCOGENE claim to have made the discovery that interleukin-6 (IL-6) "induces an epithelial-mesenchymal transition phenotype in human breast cancer cells" (Sullivan et al, 2009) and that IL-6 "promotes migration and invasion of breast cancer cells" (Walter et al, 2009). Specifically, Sullivan et al (2009) write "To our knowledge, this is the first study that shows IL-6 as an inducer of an EMT phenotype in breast cancer cells and implicates its potential to promote breast cancer metastasis." I write to point out that this claim is incorrect and is anticipated by work carried out between 1988 and 1995 in the laboratories of Dr. Igor Tamm of The Rockefeller University (Tamm et al, 1989, 1991a, 1991b, 1994a, 1994b, 1998; Krueger et al, 1991; Sehgal and Tamm, 1991) and of Dr. Michel Revel of The Weizmann Institute (Chen et al, 1988, 1991). Indeed, three of the four cell lines now investigated by Sullivan et al (2009) – T47D, ZR-75-1 and MCF-7 – were extensively investigated by Tamm and colleagues and by Revel and colleagues with the discovery, already in 1989–1994, that IL-6 induced loss of cell-cell adhesion, epithelial to mesenchymal transformation (EMT; also called "epithelioid to fibroblastoid transformation") and increased motility of breast cancer cells. IL-6 inhibited, enhanced or had no effect on epithelial cell proliferation depending on cell type and subclone characteristics (Chen et al, 1988, 1991; Tamm et al, 1989, 1994a; Krueger et al, 1991).

In painstaking experiments typically extending over 9–10 days, Tamm and colleagues used time-lapse cinemicrophotography of IL-6-treated T47D and ZR-75-1 cell lines and subclones of ZR-75-1 to observe and document the epithelial to fibroblastoid transformation of breast cancer cells in response to IL-6. In these experiments untreated T47D cells in insulin-supplemented medium formed flat epithelioid colonies with tightly apposed cell-cell junctions while ZR-75-1 cells in estradiol-17β-supplemented medium formed multilayerd three-dimensional epithelioid colonies. IL-6 dispersed these colonies accompanied by "epithelioid to fibroblastoid" transformation (Tamm et al, 1989; Tamm et al, 1991a). The titles of the respective Tamm et al articles published between 1989 and 1994 cited in the

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reference list below are in themselves informative. This body of work was summarized in 1991 as follows – “In these [ZR-75-1 and T-47D] breast carcinoma cells, IL-6 elicits a major change in cell phenotype which is characterized by a fibroblastoid morphology, enhanced motility, increased cell-cell separation, and decreased adherence type junctions (desmosomes and focal adhesions). The new data identify IL-6 as a regulator of epithelial cell growth and of cell-cell association” (Krueger et al, 1991). IL-6-treated T47D cells showed loss of vinculin, desmoplakin I/II, decreased F-actin stress fibers, perinuclear retraction of cytokeratin filaments and diminished intercellular keratin filament connections and cytokeratins (Tamm et al, 1989). Neutralizing antibodies to IL-6 inhibited the epithelioid to fibroblastoid transformation (Tamm et al, 1989; 1991a, 1991b). Similarly, Revel and colleagues, working with MCF-7, T47D and SK-BR-3 human breast carcinoma cells and clonal derivatives of T47D, reported “IL-6 induces a morphological change with loss of epithelial characteristics and cell-cell adhesion” (Chen et al, 1991). IL-6 but not TGF-α, TGF-β_1, acidic FGF, basic FGF, EGF nor IGF-I produced this transformation when assayed under serum-containing culture conditions (Tamm et al, 1991b). The phenotypic changes elicited by IL-6 on the social behavior of breast cancer cells were distinct from the inhibitory effects of IL-6 on cell proliferation and DNA synthesis (Tamm et al, 1989; 1991b). A subclone of ZR-75-1 whose proliferation was unaffected by IL-6 continued to exhibit the “cell-adhesion-disruption” phenotype in response to IL-6 (Tamm et al, 1994a). IL-6-treated subclones of ZR-75-1 cells showed decreased E-cadherin at their surfaces not involved in cell-cell contacts (Tamm et al, 1994b).

In 1990, commenting on the then Tamm observations I wrote, “The IL-6-induced phenotypic change, which is reversible, is of interest because (i) this change resembles that which certain epithelial cells undergo in early embryogenesis as they detach from the epithelium, move, and become mesenchymal in character, and (ii) it raises the question whether such changes may play a role in the invasiveness and metastasizing ability of tumor cells” (pg. 186 in Sehgal, 1990). The backdrop to that commentary was the discovery, already in 1988–1989, that IL-6 was an almost invariant presence at the host-tumor interface in human solid tumors (including mammary adenocarcinoma) with both the tumor cells and stroma showing “strong-to-moderate” IL-6 immunoreactivity (Tabibzadeh et al, 1989; Sehgal, 1990, 1998). That some human breast cancer cell lines produced IL-6 constitutively has been known for the last two decades (Tabibzadeh et al, 1989; see Chiu et al, 1996 for one confirmatory example). That transforming mutants of p53 upregulated the IL-6 promoter but wild-type p53 inhibited the IL-6 promoter suggested one possible mechanism for dysregulated autocrine production of IL-6 by cancer cells (Margulies and Sehgal, 1993).

With the increased emphasis today on the interplay between infection and cancer, and with IL-6 now identified as a major participant in that interplay (Sehgal, 1990, 1998; Bromberg and Wang, 2009 and citations therein), the recent articles of Walter et al (2009) and Sullivan et al (2009) confirm and recapitulate the concepts about the involvement of IL-6 in breast cancer pathobiology already enunciated by the Tamm and Revel laboratories between 15 to 20 years ago, but without acknowledgement of the existence of that extensive prior literature.

The following is a quotation from *A Biographical Memoir* of Dr. Igor Tamm (1922–1995) written for the National Academy of Sciences of the United States of America by Dr. Purnell W. Choppin (Choppin, 2007): “His last work focused on the role of interleukin-6 on normal and cancer cells and showed that this cytokine decreases the cell-to-cell adhesion of human ductal breast carcinoma cells. Knowledge of this kind has significance for an understanding of the metastasis of cancer cells.” The articles cited in that *Biographical Memoir* include Tamm et al 1989, 1994a, 1994b listed below.

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