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Inflammatory chemokines in breast cancer: Regulation by genetic and host factors

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Inflammatory chemokines, including CCL2, CCL5, and CXCL8 are major contributors to breast malignancy, acting at many different levels. We have analyzed the regulation of CCL2 and CCL5 expression by inflammatory cytokines in breast tumors. Our analyses indicated that TNFα and IL-1β are expressed by the tumor cells in 90% of breast cancer patients, and that both cytokines potently up-regulated the release of CCL2 and CCL5 by breast tumor cells and by normal breast epithelial cells that are as yet non-transformed. Also, we found that TNFα and IL-1β act directly on breast tumor cells and on non-transformed breast epithelial cells to promote cell characteristics leading to increased invasiveness. Combined with additional findings, we suggest that TNFα and IL-1β from autocrine sources are important up-regulators of CCL2 and CCL5 release in early and advanced stages of disease, as well as of progression-related processes. In parallel, we have analyzed the roles played by genetic and signaling components in the regulation of CCL2, CCL5 and CXCL8 in model systems of fibroblasts and of breast tumor cells. In this part, we focused on two components that undergo oncogenic deregulation in breast cancer, namely the tumor suppressor p53 and the Ras signaling pathway. Our findings provide evidence to intricate modes of interaction between p53, Ras and the chemokines, suggesting that inappropriate regulation of these genetic and signaling components promotes the release of pro-malignancy chemokines in breast cancer. Overall, our findings indicate that cooperation between inflammatory mediators and genetic/signaling components in breast cancer support breast tumor growth and metastasis.

Biography

Dr. Ben-Baruch completed her Graduate studies in Tel Aviv University, Israel. Following her post-doctoral studies at the NIH she returned to Tel Aviv University as a Faculty member, where she started analyzing the roles of chemokines in malignancy. Dr. Ben-Baruch's laboratory was the first to identify the chemokine CCL5 as a key factor supporting breast malignancy. Dr. Ben-Baruch's research has contributed to the current understanding of the role of inflammatory chemokines, primarily of CCL2 and CCL5 in breast cancer. It is now agreed by leading investigators in the field that these chemokines are key detrimental factors in breast cancer that could serve as potential targets for therapy, and for identification of patients-at-risk.