Title: Cessation of Dormancy Involves an Increase of the Expression of TGFβ1 at Protein Level in Breast Cancer

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Abstract:
Regardless of the vast progress made in the diagnosis and treatment of breast cancer, distant metastases remain the main cause of breast cancer-related deaths. A long-standing observation has shown that patients whose primary tumors had been successfully treated could neverless metastasize many years later.
In 1934, Rupert Willis postulated that ”neoplastic cells,” which have escaped from the primary tumor, must have lain dormant in the tissues in which they were arrested. He proposed that after a period of dormancy, some tumor cells may be woken up due to a change in the surrounding tissue, leading to a loosening of the growth restriction caused by the tissue.
The investigation and understanding of the tumor dormancy phenomenon may help us to resolve problems in studies concerning the cancer metastasizing and find out therapy models to prevent the escape of dormancy.
We have investigated the mechanisms of the phenomenon of dormancy in breast cancer since 2006. In this effort, we have identified important differences in the tumor cells and in the microenvironment between primary tumors and corresponding metastatic lesions and between core needle biopsy samples and the corresponding resected tumors.
The duration of dormancy in breast cancer after removing the primary tumor is unpredictable and depends on the properties of the malignant epithelial cells and on the immunological response of the host. In this study, we investigated the role of TGFβ signaling in tumor progression by estimating the expression of TGFβ1, TGFβ2, and TGFβ3 at the protein level in primary tumors and their corresponding recurrences. The frequency of Foxp3 transcription factor-positive T cells was also evaluated.
We used 137 paraffin fixed samples of primary breast cancers and their corresponding recurrent lesions, first recorded 0-2, 5-10, and >10 years after the diagnosis. The results showed that the expression of TGFβ1 was significantly higher in the recurrent lesions than in the primary tumors, regardless of tumor type and state. The frequency of intratumoral Foxp3 positive lymphocytes was associated with the tumor cell expression of TGFβ1 in the primary tumors. The protein level expression of neither of the TGFβ isoforms nor Foxp3 predicted the duration of the dormancy. In primary tumors, TGFβ1 is associated with lobular histology, ER and PR positivity, and a low grade; TGFβ2 with a smaller tumor size; and TGFβ3 with the ductal type of the tumor, a high expression of Ki67 and HER2 positivity.

Biography:
Dr. Kristiina Joensuu was born on June 18, 1948, in Nokia, Finland. She completed her matriculation examination in Kemi, Finland, on May 31, 1967, before pursuing medical studies at the University of Bern in Switzerland, where she earned her medical degree on September 24, 1975. After graduation, she began her medical career as a general practitioner in Hollola, Finland, serving from 1975 to 1978. She later specialized in pathology, completing her specialist examination at the University of Tampere on February 26, 1982.

Her career as a pathologist includes over two decades as a departmental pathologist in the Hospital District of Päijät-Häme, Finland, from July 1982 to October 2003. She subsequently became the Chief Physician of Pathology at the Southeastern Hospital District (Carea) in Finland. Her academic achievements continued with her PhD dissertation on "Tumor Dormancy in Breast Cancer," which she defended at the University of Helsinki on October 12, 2012, and received her PhD degree on February 12, 2013.

Since 2013, Dr. Joensuu has been a senior researcher in the breast cancer research group led by Professor Päivi Heikkilä in the Department of Pathology at the University of Helsinki. Her research focuses on the phenomenon of tumor dormancy in breast cancer, utilizing archival formalin-fixed breast cancer samples. Her team analyzes changes in immunohistochemical protein expression in early- and late-relapsing primary tumors, recurrent/metastatic tumors, and core needle biopsies of primary tumors alongside their surgical resection specimens. This work includes evaluating protein expression both in tumor cells and in the surrounding tumor microenvironment.

Her latest research, published in *Pathology - Research and Practice* in 2024, examines the expression of Transforming Growth Factor Beta (TGF-β) and the distribution of CD4 and CD8 T cells in core needle biopsies and surgical resection samples of primary breast cancer. The article, co-authored by Joensuu, Heiskala, and Heikkilä, investigates how core needle biopsy may alter TGFβ1 and TGFβRII protein expression and immune cell distribution in breast cancer tissues. Additionally, her ongoing work explores immunohistochemical analysis of virus-related antibodies, including Anti-BLV p24, Mouse Anti-MMTV, Anti-HPV16 E6+HPV18E6, and Anti-EBNA-1, in primary and recurrent breast cancer tumors to assess potential expression differences between primary and metastatic samples.

Dr. Joensuu has been married since 1971 and has a family of four adult children and eleven grandchildren. She continues to advance breast cancer research as a postdoctoral researcher at Medicum, Department of Pathology, University of Helsinki, alongside her collaborators Professor Päivi Heikkilä and Dr. Marja Heiskala.