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Granulin:Cyclin T1 Interactions in Breast Cancer

[We will define the role in breast cancer of interactions between a growth factor granulin precursor and cyclin T1, component of the transcription factor P-TEFb]

Granulins are increasingly recognized as an important family of cellular growth factors. One member of this family, the granulin/epithelin precursor (GEP), has been implicated in aspects of tumor formation (tumorigenicity). In human breast carcinomas that are insensitive to the hormone estrogen, GEP is highly expressed. Experimental treatment that inhibited its expression resulted in almost complete loss of tumorigenicity in cell cultures and in mice. This suggests that high levels of GEP expression are responsible for breast cancer cell malignancy. In addition, stimulation of GEP production in estrogen-sensitive breast cancer cells led to loss of estrogen sensitivity. This observation indicates that GEP plays a role in the transition from estrogen-responsive to estrogen-unresponsive breast carcinoma, a critical step in the development of breast cancer with poor prognosis.

We recently established a connection between GEP and the control of transcription, an essential step in gene expression which, if dysregulated, can lead to cancer. Our studies uncovered a novel biochemical interaction between GEP and the protein cyclin T1 inside cells. Cyclin T1, together with its kinase partner CDK9, is part of the transcription elongation factor P-TEFb. When transcription elongation was examined in normal cells of various types, we found that GEP repressed gene expression that depends on P-TEFb. No such inhibition was seen in cells that express high levels of GEP. These observations suggest a mechanism that could explain the role of GEP in breast cancer. High levels of GEP expression might cause the loss of its transcription repression activity and thereby facilitate malignant transformation. In this proposal, we plan to explore this hypothesis. This work will help understand the function of a tumor-related growth factor in the genesis and progression of breast cancer, and could lead to the development of novel therapies.