Karolinska Institutet

Department of Women's and Children's Health

Search for Markers and Molecular Mechanisms of Aggressive Endometrial Cancer: Profiling of Aggressive vs Non-Aggressive Endometrial Cancers

AKADEMISK AVHANDLING
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ABSTRACT

Endometrial cancer is the seventh frequent type of cancer among women. Identification of new prognostic markers is important to optimize treatment and follow-up of all EC patients. Understanding the molecular mechanisms of carcinogenesis may pave through discovery of further EC molecular markers.

Cohort studies often disregard the individual features of tumors. Since such features may represent an opportunity to individualize cancer treatment, an innovative approach for their assessment should be developed. In this study (paper I), we addresses the previously overlooked individual characteristics of endometrial cancers, which could serve as a wellspring of information regarding specific molecular processes; regulators of such processes could potentially be useful for predicting aggression in individual endometrial tumors. Systemic analysis of individual proteome profiles represented that different proteins may be impacted in the individual endometrial tumors of different patients, but the impact of these proteins on basic cell functions may still be similar. The correlation between publically available gene expression data sets of profiling of endometrial tumors and our proteome profiling supports the conclusion that individual tumor features are doubtlessly crucial in endometrial tumorigenesis and are not inconsistent individual variations. IHC validation using tissue microarray analysis of MST1 and PKN1 proteins suggested their potential to serve as predictive biomarkers for endometrial cancer as well as efficacy of this approach.

Transforming growth factor-β (TGFβ) and epidermal growth factor (EGF) are two potent regulators of tumorigenesis. Signaling cross-talk between TGFβ and EGF involves a number of regulators which define the impact on cell physiology (Paper II and III). In paper II, we discuss mammalian sterile-like 1 kinase (MST1) as a negative regulator of combined TGFβ and EGF signaling. We observed that enhanced expression of MST1 inhibited the combined action of TGFβ1 and EGF on cell invasiveness, migration and proliferation. Monitoring of the intracellular regulatory proteins showed that the MST1 contribution to TGFβ-EGF cross-talk may involve focal adhesion kinase and E-cadherin, but not activation of Smad2. Our data elucidated the negative feedback role of MST1 on TGFβ1‑ and EGF−regulated cell invasiveness, migration and proliferation.

Our results from paper III demonstrated that protein kinase N1 (PKN1) modulated responses of HEC-A-1 endometrial cancer cells to TGFβ1 and EGF. PKN1 had an inhibitory effect on stimulation of cell migration, and PKN1 kinase activity was required for the inhibitory effect of TGFβ and EGF on cell proliferation and invasiveness. We observed that phosphorylation of Smad2, FAK and Erk1/2 correlated with cellular response to TGFβ1 and EGF. PKN1 modulates TGFβ and EGF-dependent regulation of cell proliferation, migration and invasiveness, and is therefore a component of the signaling network downstream of TGFβ and EGF.

Thus, our findings provided insights into different mechanisms of tumorigenesis and on the impact of cross-talk between signaling pathways on tumor development.

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