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Review

Odyssey of trefoil factors in cancer: Diagnostic and therapeutic implications

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ABSTRACT

Trefoil factors 1, 2, and 3 (TFFs) are a family of small secretory molecules involved in the protection and repair of the gastrointestinal tract (GI). TFFs maintain and restore epithelial structural integrity *via* transducing key signaling pathways for epithelial cell migration, proliferation, and invasion. In recent years, TFFs have emerged as key players in the pathogenesis of multiple diseases, especially cancer. Initially recognized as tumor suppressors, emerging evidence demonstrates their key role in tumor progression and metastasis, extending their actions beyond protection. However, to date, a comprehensive understanding of TFFs' mechanism of action in tumor initiation, progression and metastasis remains obscure. The present review discusses the structural, functional and mechanistic implications of all three TFF family members in tumor progression and metastasis. Also, we have garnered information from studies on their structure and expression status in different organs, along with lessons from their specific knockout in mouse models. In addition, we highlight the emerging potential of using TFFs as a biomarker to stratify tumors for better therapeutic intervention.

1. Introduction

Trefoil factors (TFFs), TFF1, TFF2 & TFF3 are well established for their involvement in mucosal repair from a variety of environmental insults including acid, microbes and microbial products. The epithelium of the gastrointestinal (GI) tract naturally produces TFFs to combat endless pathogenic and microbial attacks as the natural defense mechanism [1]. These TFFs influence cell-cell contact and cell migration to damaged areas during wound repair [2]. Besides their role in protection and restitution of the GI tract, TFFs also play critical roles in carcinogenesis. While earlier studies using biochemical and genetic mouse models described tumor suppressor functions of TFFs, recent intriguing evidence from experimental and clinical studies suggest that they play a proto-oncogenic role in many solid tumors. In addition, the clinical utility of TFFs as potential biomarkers is emerging in various diseases, including cancer. While the importance of TFFs in GI defense is extensively studied, the molecular and cellular mechanisms of their action in cancer initiation and progression remain largely unknown. Herein, we have comprehensively reviewed the recent findings on the molecular and clinical significance of TFFs in cancer pathogenesis.

2. TFFs expression and structure

During development, TFFs are expressed in the stomach and duodenum regions of the fetus, while no expression is observed in placental or fetal membranes [3]. Increased serum levels of TFF2 and TFF3 are observed during pregnancy. In the adult tissues, TFF1 is mainly expressed in the superficial and foveolar epithelium of salivary glands, stomach, brain, liver, kidney, and respiratory tract. In contrast to the diffuse expression of TFF1 in the stomach, TFF2 is mainly expressed by

Abbreviations: JAK/STAT, Janus kinase signal transducers and activation of transcription; GKN2, Gastrokine 2; Lnc RNA, Long non-coding RNA; CDS, Coding DNA sequence; TSS, Transcription start site; LYVE-1, Lymphatic vessel endothelial hyaluronan receptor 1; REG1A, Regenerating family member 1 alpha; AP-1, Activator protein 1; HNF3, Hepatocyte nuclear family 3; SV40, Simian vacuolating virus 40; ER, Estrogen receptor; ERBB, Avian erythroblastosis oncogene B; PRINS, Psoriasis-susceptibility-related RNA gene Induced by Stress; 2-DG, 2-Deoxy-D-glucose; TPA, Tissue plasminogen activator; MMP-9, Matrix metalloprotease; PAR, Protease-activated receptor; LacdiNAc, N,N-di-N-acetyllactose diamine

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