Abstract

Hyaluronan is a large glycosaminoglycan mainly presented in the extracellular matrix as well as in the intracellular compartment. Hyaluronan is synthesized by three hyaluronan synthase isoforms, namely HAS1, HAS2 and HAS3. HAS3v2 is a smaller splicing variant of HAS3 with 281 AA in length. Here, biological and pathological functions of HAS3v2 were investigated for the first time.

HAS3v2 localizes on membrane of the endoplasmic reticulum as shown by stable overpression of YFP-HAS3v2 fusion protein. Overexpression of HAS3v2 leads to increased intracellular hyaluronan. A HA-HAS3v2 complex was also detected in microsomes of YFP-HAS3v2 overexpressing cells using the HAS enzymatic capture assay. This indicated HAS3v2 is an intracellular hyaluronan synthase or at least HA binding protein.

Esophageal cancer is one of the 10 most frequent tumor types worldwide, which is distinguished into two major subtypes: squamous cell carcinoma (ESCC) and adenocarcinoma (EAC). HAS3v2 is upregulated only in human EAC and also correlated with TNM staging. This suggested that HAS3v2 is a potential tumor marker for EAC. Lentiviral overexpression of HAS3v2 promotes cell proliferation rate both in vitro and after xenografting of HAS3v2 overexpressing EAC cells in nude mice . This phenotype was, at least partially, caused by enhanced ERK1/2 kinase phosphorylation. HAS3v2 also stimulated the phosphorylation of focal adhesion kinase (FAK) and improve EAC cell adhesion. Both phosphorylations could be the consequence of activated RHAMM signaling. Overexpression of HAS3v2 in cancer cells also stimulated HAS3v1 mRNA expression in stromal cells of EAC xenograft, which led to increased stromal HA levels. The stromal HA has been reported to provide microenvironment in favor for progression and metastasis.

The expression of HAS3v2 in EAC was regulated by EGF pathway and the blocking antibody of EGFR, Cetuximab, diminished the EGF-induced HAS3v2 upregulation. Furthermore, the mRNA expression of HAS3v2 and EGFR are positively correlated in EAC patients.

Taken together, HAS3v2 promotes malignant tumor cell phenotype and could be a diagnostic oncogene and a potential therapeutic target for EAC.