ABSTRACT

ADAM12 (a disintegrin and metalloprotease 12) plays an important role in human physiology as well pathology including severe types of disease such as muscoskeletal disorders and cancer. Here the zebrafish is studied as a possible model organism to establish the function of ADAM12 *in vivo* by gene knock-down. Recombinant expression of the extracellular part of zebrafish ADAM12 was conducted using mammalian and *Escherichia coli* cells. The enzyme was expressed both in mammalian cells and *E. coli*. However, functional characterization could not be conducted because the expressed enzyme was inactive or inappropriately processed. Human ADAM12 plays a role in shedding of EGFR ligands from the cell surface. Therefore, the role of zebrafish ADAM12 lacking the cytoplasmatic domain but retaining the transmembrane region was cloned. The data showed that zebrafish ADAM12 including the transmembrane region was expressed at the cell surface of CHO K1 cells after transfection. Furthermore, the enzyme was proteolytically active because it released EGF from cell-membrane bound proEGF. These data indicated that zebrafish ADAM12 is an active sheddase at the cell surface. Two human membrane-type matrix metalloproteases, namely MT1- and MT2-MMP are highly important molecules, both involved in the progression and spread of human cancer. Using an experimental setup similar to that used for transmembrane zebrafish ADAM12, it was shown here for the first time that both MT1- and MT2-MMP are highly active in proEGF ectodomain shedding. Signalling through the EGF receptor is important for normal development and its dysregulation are directly linked to cancer. The inhibition of this pathway may represent a novel target to suppress both ADAM12 and MMP-dependent processes associated with tumor cell initiation and progression.