

Inhibition of EpCAM cleavage as an alternative and synergistic approach in cancer therapy

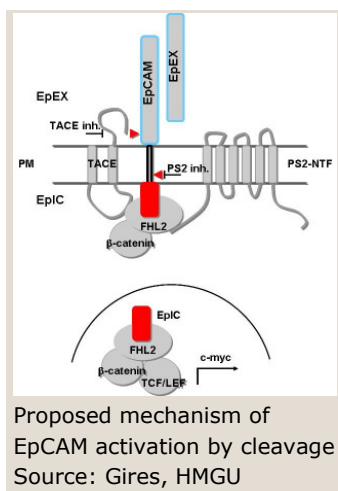
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Challenge

Cancer is characterized by uncontrolled division of cells and the ability of these cells to invade other tissues. One approach of cancer therapy included targeting of the epithelial cell adhesion molecule EpCAM, a type I transmembrane glycoprotein. Accordingly, a variety of effective cancer therapy strategies and clinical trials make use of EpCAM as a target molecule for (single chain) monoclonal and bispecific antibodies.

The elucidation of mechanisms and factors responsible for the regulation of EpCAM at the transcriptional level is a further field of interest. Inhibition of EpCAM with anti-sense mRNA or siRNA resulted in a strongly decreased proliferation of head and neck as well as breast carcinoma cells along with a diminished migration and invasion *in vitro*. Unveiling the mechanisms of EpCAM activation and signal transduction offers the possibility of specific inhibition of EpCAM signaling.

Technology



It has been found that the signal transduction of EpCAM involves proteolytic cleavage and shedding of a large extracellular ectodomain, and the release of an intracellular domain (EpIC). A direct binding partner and essential signal mediator of EpIC has been identified as the FHL2 protein, which links EpCAM to the β -catenin/TCF/Lef pathway. It has been demonstrated that the mechanism of EpCAM cleavage requires the binding and proteolytic activity of TACE and presenilin-2 (PS-2). Specific inhibition of EpCAM cleavage, by inhibiting TACE or PS-2, results in a functional down-regulation. Inhibitors of both proteases were effective repressors of EpIC formation and EpCAM induced c-myc up-regulation.

Commercial Benefit and Opportunity

The activation of EpCAM opens new possibilities for therapeutic intervention and may be used to improve existing therapies, particularly those employing anti-EpCAM antibodies. First, inhibition of ectodomain shedding generates an increased number of target molecules available for therapeutic antibodies. Second, EpCAM-mediated effects are hampered upon inhibition of signal transduction downstream of EpCAM.

The technology is available for (non)-exclusive licensing. Parties interested in collaborative research and development are highly welcomed.

Developmental Status

Inhibition of TACE or presenilin-2 *in vitro* showed an increase of EpCAM molecules on the surface of cancer cells and abolished EpCAM-dependent signaling and cell proliferation *in vitro*. Animal models to prove the mechanism are currently in progress.

Patent Situation

Patent applications are pending in EP, US and SG.

Relevant Publication

Maetzel et al. (2009), Nature Cell Biol. 11, 162-171.

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