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| **(Sample)** |
| **EphA2 processing by MT1-MMP in cutaneous squamous cell carcinoma** |
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| [Objective] Invasive cutaneous squamous cell carcinoma (SCC) is considered to develop from SCC in situ (SCIS), but the developmental process is not clear. EphA2 is a member of the Eph family of receptor tyrosine kinases and interacts with ligands known as ephrins. In normal cells, binding of EphA1 to EphA2 inhibits RAS and its downstream signals, leading to suppression of the EGF- EGFR growth pathway; whereas in cancer cells, the MT1- MMP-processed form of EphA2 promotes invasion via stimulation of RAS. We previously reported possible processing of EphA2 by MT1-MMP in invasive cutaneous SCC. Here, we investigated the proximity of MT1-MMP and EphA2 on cancer cells in reference to its effect on EphA2 processing and relationship with tumor invasiveness. [Methods] Expression patterns and levels of EphA2 (C-term and N-term) and MT1-MMP were immunohistochemically analyzed from samples of invasive SCC and SCIS. The proximity of MT1-MMP and EphA2 to cancer cells and their effect on EphA2 processing were investigated using a combination of in situ PLA (Proximity Ligation Assay) and Western blotting. [Results] Immunohistochemical study showed that expression levels of C- and N-term of EphA2 were similar in SCIS, while expression levels of N-term of EphA2 were significantly reduced compared to those of C-term in invasive SCC. In vitro, proximity of MT1-MMP and EphA2 was demonstrated by in situ PLA in MT1-MMP expressing HT-1080 cells in association with generation of processed EphA2 fragments. In contrast, in MT1-MMP-knockdown HT-1080 cells, proximity of MT1-MMP and EphA2 was not evident and processed EphA2 fragments were decreased. [Conclusion] These lines of evidence suggest possible involvement of MT1-MMP processing of EphA2 in invasiveness of cutaneous SCC. |
| Key words: SCC, EphA2, MT1-MMP |