



Abstract

Study of the Retrotransposon-Derived Human PEG10 Protease [†]

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Abstract: Paternally expressed gene 10 (*PEG10*) is a human retrotransposon-derived imprinted gene. Previous works have demonstrated that a mutation in the coding sequence of this gene is lethal with regard to embryological age due to defects of placental development. In addition, *PEG10* is implicated in several malignancies, such as pancreatic cancer and hepatocellular carcinoma. The *PEG10* gene encodes two protein isoforms, which are translated by a typical retroviral frameshift mechanism. The Gag-like protein (RF1_{PEG10}) is encoded by reading frame 1, whilst reading frames 1 and 2 accounts for the Gag-Pol-like polyprotein (RF1/RF2_{PEG10}). The protease (PR) domain of RF2_{PEG10} contains an -Asp-Ser-Gly- sequence, which refers to the conservative -Asp-Ser/Thr-Gly- active-site motif of retroviral aspartic proteases. The function of the aspartic protease domain of RF2_{PEG10} remains unclear. In order to further investigate the function of the *PEG10* protease (PR_{PEG10}), a frameshift mutant was generated (_{fs}RF1/RF2_{PEG10}) for comparison with the RF1/RF2_{PEG10} form. To study the effects of PR_{PEG10} on cellular proliferation and viability, mammalian HEK293T and HaCaT cells were transfected with plasmids encoding for either the frameshift mutant (_{fs}RF1/RF2_{PEG10}) or a PR active-site (D370A) mutant _{fs}RF1/RF2_{PEG10}. Based on our findings, an _{fs}RF1/RF2_{PEG10} overexpression resulted in an increased cellular proliferation, compared to the mutant form. Interestingly, transfection with _{fs}RF1/RF2_{PEG10} had a detrimental effect on cell viability. We hypothesize that PR_{PEG10} may play a cardinal role in the function of this retroviral remnant, possibly implicated in cellular proliferation and the inhibition of apoptosis.

Keywords: PEG10; paternally expressed gene 10; cell viability; cell proliferation; cis protease activity; ubiquitination; homology modeling; retroviral-like protease; protease; retrotransposon



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