
Misdirected activity of antiviral proteins against syncytins

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Abstract

Syncytin-1 and syncytin-2 are envelope glycoproteins encoded by human endogenous retroviruses that have been exapted for the fusion of cytotrophoblast cells into syncytiotrophoblasts during placental development. Interestingly, pregnancy complications have been associated with altered expression of interferon-stimulated genes, including antiviral restriction factors. We therefore hypothesize that antiviral proteins may mis-target syncytins and interfere with normal placenta formation when aberrantly active during pregnancy.

In an initial screening, we tested a panel of restriction factors to determine which antiviral host proteins might inhibit syncytin-mediated fusion. In agreement with a previous study (Buchrieser et al., 2019), we found that the antiviral protein IFITM3 inhibits syncytin-1-mediated membrane fusion. Moreover, guanylate binding protein 2 and 5 (GBP2 and GBP5) suppressed fusion mediated by both syncytins, although syncytin-1 and -2 differed in their sensitivity. Furthermore, expression of GBP2 and GBP5 is interferon-inducible and driven by solo-LTRs of the ERV9 family (Srinivasachar Badarinarayan et al., 2020). In an earlier study (Braun et al., 2019), our group had shown that GBPs prevent the proteolytic maturation of viral envelope proteins by inhibiting the activity of furin. Surprisingly, we did not observe GBP-mediated suppression of syncytin-2 cleavage, whereas syncytin-1 maturation was inhibited by both GBPs. Our investigation further revealed that syncytin-2 is efficiently cleaved by PCSK7, a protease from the same protein family as furin. In contrast to furin, the proteolytic activity of PCSK7 was not inhibited by GBPs.

Overall, this study revealed that aberrant expression of antiviral factors can reduce syncytin-mediated fusion. However, syncytin-1 and syncytin-2 can be processed by several host proteases, which may partially compensate for impaired cleavage in the presence of GBPs. Altogether, our results provide insights into pathological placenta formation as a result of innate immune responses that are misdirected against endogenous retroviral proteins.

Keywords: endogenous retrovirus, syncytin, cell fusion, antiviral proteins, guanylate binding proteins

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