ASCT2, but not ASCT1, is a functional receptor for Syncytin-1-induced cell fusion

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Abstract

Syncytin-1, a human protein of retroviral origin, is a remnant of an ancient infection. It has been exapted to fulfill a crucial role in human placenta morphogenesis. After the interaction with transmembrane protein ASCT2 (Alanine, Serine, Cysteine Transporter 2), Syncytin-1 triggers cell-to-cell fusion of trophoblasts into syncytiotrophoblast, the outermost layer of the human placenta. Dysregulation of Syncytin-1 has been implicated in various placental pathologies, including preeclampsia, low platelets syndrome, and intrauterine growth restriction.

Another transmembrane protein, ASCT1, has been proposed as an alternative cellular receptor for Syncytin-1. Together with the structurally similar ASCT2, both proteins have been reported as receptors for the RD114 and D-type retroviruses (RDR) interference group. However, the extent of their involvement in Syncytin-1-induced cell-to-cell fusion and their preference for RDR retroviruses require further investigation.

In this study, we examined the individual roles of ASCT1 and ASCT2 as receptors for Syncytin-1 using three quantitative assays. We compared the infection efficiency of Syncytin-1-pseudotyped virus on cells expressing either ASCT1 or ASCT2. Additionally, we evaluated the binding affinity of Syncytin-1 to ASCT2 and ASCT1 on the cell surface and, finally, assessed the fusogenic activity of Syncytin-1 following interaction with each receptor.

Our results indicate that ASCT1 exhibits at least two orders of magnitude lower receptor activity compared to ASCT2, casting doubt on its significance in syncytiotrophoblast differentiation. These findings underscore the pivotal role of ASCT2 in placental development and raise questions about the physiological relevance of ASCT1 in Syncytin-1-induced cell fusion.

Keywords: ASCT1, ASCT2, envelope, fusion, HERV, placenta, receptor, retrovirus

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