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Hes-1-targeting siRNA inhibits the maturation of murine myeloid-derived dendritic cells

Research Article

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Abstract: Activation of Notch by Jagged-1 may plays a pivotal role in maturation of dendritic cells (DCs), but the mechanism has not been completely defined. In the present study, Hes-1 (Hairy/enhancer-of-split)-targeting siRNA was used to confirm a role of Jagged-1-Notch signaling pathway activation in maturation of murine bone marrow-derived DCs and to search for a target that plays a critical role. The results showed that compared with the control, lipopolysaccharide or Zymosan A groups, Jagged-1 (a soluble Jagged 1/Fc chimera protein) effectively increased expression of Hes-1 and Deltex-1 mRNA, which could be reversed by DAPT (2, 4-diamino-5-phenylthiazole), a specific inhibitor of the Notch signaling pathway. Hes-1-targeting siRNA could successfully down-regulate the endogenous Hes-1 expression in the DCs. Concurrently, a significant down-regulation of CD40, CD80, CD86 and MHC-II expressions on the surface of the DCs was found with the reduction of IL-12 yielded by the DCs. Our results demonstrate that Hes-1-targeting siRNA can inhibit the maturation of the DCs induced by Jagged-1, indicating Hes-1 may be an important target of Notch signaling mediating the maturation of DCs.

Keywords: *Jagged-1 • Hes-1 • siRNA • Dendritic cell • Maturation*

1. Introduction

Dendritic cells (DCs) are antigen-presenting cells with critically important functions in innate and adaptive immunity. Notch signaling plays an important role within hematopoietic and immune systems. Depending on cell types, Notch signaling can positively or negatively influence proliferation, differentiation, and apoptosis [1,2]. Current studies suggest that Notch-ligand interactions result in cleavage of the intracellular domain of Notch (NICD) and translocation of NICD to the nucleus where it interacts with the transcriptional repressor CSL(RBP-Jκ). Binding of NICD displaces co-repressor complexes, thereby activating transcription by promoters with CSL (CBF1, Su(H) and LAG-1) binding element [3-5].

Jagged-1, a single trans-membrane glycoprotein, is one of the major ligands for Notch receptors on the mammalian cell membrane, and expressed on many tissue cells, such as bone marrow, fetal liver stroma and thymus epithelium. It participates in controlling growth, developing numerous tissues and maintaining renewal and differentiation of normal haemopoietic stem cells [6]. Jagged-1 is also expressed highly on the surface of antigen presenting cells (APC), such as dendritic cells, B cells and macrophages. It can promote maturation of DCs [7] and Notch signaling can maintain and control differentiation of $CD8^-$ DCs [8], suggesting that Jagged-1-Notch signaling possibly plays an important part in an immune response.

Hes-1 (hairy enhancer of split-1) is known to code for a basic helix-loop-helix transcription factor [9]. Hes-1 protein binds to its own promoter and negatively regulates its activity by binding N-box domains located in the promoter region of Hes-1 [10-12]. Hes-1 transcriptional up-regulation is perhaps the best characterized function

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