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• 中文摘要

Notch 蛋白爲細胞表面的受體，在結構上具有高度保留性，對於細胞命運的決定，以及前驅細胞數量、特性的保持，都扮演著相當重要的角色。隨著細胞種類的不同，受體的活化作用參與有關細胞分化、增生與凋亡的不同調控角色。目前已知的 Notch 訊號傳遞路徑爲：藉由與相鄰細胞的 Ligand 結合，Notch 受體被活化而導致此蛋白被分解，此時 Notch 受體細胞內區域被釋出，並且移動到細胞核中，與核內細胞因子作用，促使訊號往下傳遞。藉由轉錄因子 CBF1 有關或 CBF1 無關的兩種方式，Notch 受體細胞內區域可活化下游基因的表現。Notch 訊號傳遞路徑的調控相當複雜，截至目前仍混沌不清。雖然已發現一些 Notch 1 受體細胞內區域(N1IC)的結合蛋白，位於細胞中不同的位址，活化或抑制 Notch 訊號傳遞路徑，但仍無法得知詳細的分子調控機制。本實驗室於先前已進行 N1IC 的結合蛋白之篩選及鑑定工作，研究發現：在人類 Jurkat 以及 T-cell acute lymphoblastic leukemias (T-ALL)兩種細胞內，內生性的 Notch 1 受體細胞內區域都會與細胞內轉錄因子 YY1 結合，而且在細胞核中形成很大的 Complex。更進一步研究顯示：N1IC 可活化具有 CBF1-response elements 的 Promoter activity，經由此結合作用，這個活化現象會被轉錄因子 YY1 所抑制。N1IC 藉由與 CBF1 蛋白結合，而可以結合在 CBF1-response elements 的 DNA 上；轉錄因子 YY1 也藉由與 N1IC 結合，而間接結合在此 DNA 上。

• 英文摘要

Notch genes encode evolutionarily conserved receptors that have been utilized to control cell fate decisions during development. Notch signaling participates in several cellular functions such as proliferation, apoptosis, and differentiation, depending upon the cellular context of Notch activation. In the prevailing model for Notch signaling, Notch receptors are activated through binding with ligands on neighboring cells. Notch intracellular domains are released and translocated into nucleus after proteolytic cleavages triggered by ligand binding. Then Notch intracellular domains activate the expression of their target genes via both CBF1-dependent and -independent pathway. The control of Notch signaling is very complicated and not fully understood yet. So far, there are

several Notch 1 receptor intracellular domain (N1IC)-associating cellular factors that were identified to modulate the Notch signaling both positively and negatively. These data indicate that the activity of Notch signaling is modulated by different cellular factors in different subcellular compartments. Though the members of Notch-associated factors and the downstream target genes are expanding, the molecular mechanisms of Notch signaling in diverse developmental systems remain unsolved. In the previous study, we had screened and characterized the N1IC-associating proteins. The transcription factor Ying Yang 1 (YY1) was identified to associate with N1IC in a high-molecular-weight complex in nucleus and this association modulated the CBF1-dependent gene expression. Furthermore, YY1 indirectly regulate the transcriptional activity of the wild-type CBF1 response elements via the direct interaction of N1IC and CBF1. We also demonstrated the association between endogenous N1IC and intrinsic YY1 in both of the human Jurkat cells and acute T cel lymphoblastic leukemia (T-ALL) cells. Taken together, these results indicate transcription factor YY1 may modulate Notch signaling via association with the large Notch complex.