Available online at www.sciencedirect.com

Metabolism

www.metabolismjournal.com

Clinical and experimental aspects of notch receptor signaling: Hajdu-Cheney syndrome and related disorders

*Ernesto Canalis**

Department of Orthopaedic Surgery, the UConn Musculoskeletal Institute, UConn Health, Farmington, CT 06030, USA
Department of Medicine, the UConn Musculoskeletal Institute, UConn Health, Farmington, CT 06030, USA

ARTICLE INFO

Article history:
Received 13 June 2017
Accepted 13 August 2017

Keywords:
Hajdu Cheney Syndrome
Genetic disorders
Notch
Osteoporosis
Acroosteolysis

ABSTRACT

Background. There are four Notch transmembrane receptors that determine the fate and function of cells. Notch is activated following its interactions with ligands of the Jagged and Delta-like families that lead to the cleavage and release of the Notch intracellular domain (NICD); this translocates to the nucleus to induce the transcription of Notch target genes. Genetic disorders of loss- and gain-of-NOTCH function present with severe clinical manifestations.

Basic Procedures. In this article, current knowledge of Hajdu Cheney Syndrome (HCS) and related disorders is reviewed.

Main Findings. HCS is a rare genetic disorder characterized by acroosteolysis, fractures, short stature, neurological manifestations, craniofacial developmental abnormalities, cardiovascular defects and polycystic kidneys. HCS is associated with *NOTCH2* gain-of-function mutations. An experimental mouse model of the disease revealed that the bone loss is secondary to increased osteoclastogenesis and bone resorption due to enhanced expression of receptor activator of nuclear factor kappa B ligand (Rankl). This would suggest that inhibitors of bone resorption might prove to be beneficial in the treatment of the bone loss associated with HCS. Notch2 is a determinant of B-cell allocation in the marginal zone of the spleen and "somatic" mutations analogous to those found in HCS are associated with B-cell lymphomas of the marginal zone, but there are no reports of lymphomas associated with HCS.

Conclusion. In conclusion, HCS is a serious genetic disorder associated with *NOTCH2* mutations. New experimental models have offered insight on mechanisms responsible for the manifestations of HCS.

Abbreviations: ANK, ankyrin; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CSL, CBF1, Suppressor of Hairless Lag 1; CHYS1, chondroitin sulfate synthase; Dll, Delta-like; EGF, epidermal growth factor; EOGT, EGF domain specific O-linked N acetylglucosamine transferase; HCS, Hajdu Cheney Syndrome; Hes, hairy and enhancer of split; Hey, HES-related with YRPW; HD, heterodimerization domain; Jag, Jagged; LP, leader peptide; LFNG, Lunatic fringe; LMS, Lateral Meningocele Syndrome; LNR, LIN-12 Notch repeats; MZ, marginal zone; Maml, mastermind-like; MESP, mesoderm posterior bHLH transcription factor; μCT, microcomputed tomography; NRR, negative regulatory region; NICD, Notch intracellular domain; NLS, nuclear localization sequence; PEST, proline (P), glutamic acid (E), serine (S) and threonine (T); RAM, Rbpjκ-association module; Rankl, receptor activator of nuclear factor kappa B ligand; Rbpjκ, recombination signal-binding protein for Ig of κ region; TMD, transmembrane domain.

* Department of Orthopaedic Surgery and Medicine, UConn Health, Farmington, CT 06030-5456, USA.
E-mail address: canalis@uchc.edu.

http://dx.doi.org/10.1016/j.metabol.2017.08.002
0026-0495/

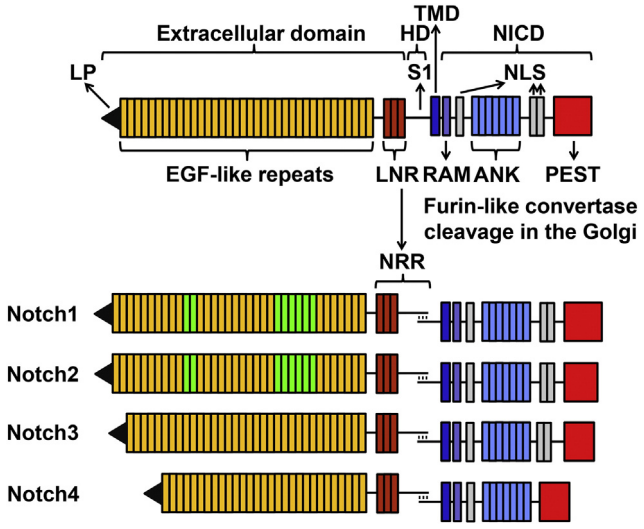

Fig. 1 – Domains of the four Notch receptors. The upper panel shows the domain and motif organization of a generic human/murine Notch receptor before cleavage at the S1 site by furin-like convertases in the Golgi compartment. The extracellular domain contains a leader peptide (LP) and multiple epidermal growth factor (EGF)-like tandem repeats followed by Lin12-Notch repeats (LNR) and the heterodimerization domain (HD). The transmembrane domain (TMD) is located between the extracellular and intracellular domains. The Notch intracellular domain (NICD) contains an Rbpjκ-association module (RAM), a nuclear localization sequence (NLS), ankyrin (ANK) repeats and tandem NLS, which are followed by a proline (P)-, glutamic acid (E)-, serine (S)- and threonine (T)-rich (PEST) domain. The lower panel shows the domains and motifs of heterodimeric individual receptors, the negative regulatory region (NRR) is formed by the LNR and HD following cleavage at the S1 site. Notch1 and Notch2 have 36 EGF-like repeats; in green are those required for binding of Notch1 and Notch2 to cognate Delta/Serrate/Lag2 ligands. Notch1 and Notch2 have a similar NICD, and Notch3 has 34 EGF-like repeats and a shorter NICD than Notch1 and Notch2. Notch4 has 29 EGF-like repeats and an NICD that is shorter than that of other receptors and lacks the tandem NLS located between the ANK repeats and the PEST domain. Reproduced with permission from Zanotti and Canalis, Endocrine Reviews 37:223, 2016.

1. Notch Receptors

Notch has emerged as a novel signal that plays a key role in cell fate decisions and in the differentiation and function of cells of multiple lineages. There are four Notch receptors (Notch1 to 4) and five classic Notch ligands termed Jagged (Jag)1 and Jag2, and Delta-like (Dll)1, Dll3 and Dll4 [1]. Notch and its ligands are transmembrane proteins that retain structural similarity and mediate communication between neighboring cells. The extracellular domain of Notch is the site of interaction with its ligands, and consists of multiple epidermal growth factor (EGF) repeats. At the junction of the extracellular and the transmembrane domain of Notch rests the negative regulatory region (NRR). This is the site of cleavage required for the initial activation of Notch following its interactions with Jag or Dll ligands [2,3]. The intracellular domain of Notch (NICD) consists of an Rbpjκ-association module (RAM) domain, ankyrin repeats and nuclear localization sequences. These domains are required to induce the transcription of Notch target genes [4,5]. The C-terminus of Notch contains a proline (P)-, glutamic acid (E)-, serine (S)-, threonine (T) (PEST) domain, which is targeted by ubiquitin ligases. This domain is required for the proteasomal degradation of Notch (Fig. 1). Notch ligand interactions lead to its proteolytic cleavage and the release of the NICD, and its translocation to the nucleus, where it forms a complex with recombination signal-binding protein for Ig of κ region (Rbpjκ) and mastermind-like (Maml) to regulate transcription [6–8]. The human ortholog of Rbpjκ is termed CBF1, Suppressor of Hairless, Lag 1 (CSL) [9]. The interaction of the NICD, Rbpjκ and Maml leads to the displacement of transcriptional repressors and recruitment of activators of transcription by the NICD to induce the expression of Notch target genes (Fig. 2). This has been termed the Notch canonical signaling pathway, and results in the induction of hairy and enhancer of split (Hes)1, Hes5, Hes 6 and Hes7, and HES-related with YRPW motif (Hey)1, Hey2 and HeyL [10–12]. Importantly Rbpjκ, and not the NICD, binds to DNA. Although Rbpjκ acts as a transcriptional activator in Notch signaling, in the absence of Notch-ligand interactions Rbpjκ acts as a transcriptional repressor due to its ability to recruit transcriptional co-repressors and histone deacetylases. This complex is disrupted by the NICD, leading to the recruitment of co-activators of transcription, histone acetylation and enhanced transcription of target genes [13,14]. Cyclin-dependent kinase 8 phosphorylates the PEST domain of the NICD, causing the disassembly of the ternary NICD, Rbpjκ, Maml complex followed by the ubiquitination of the NICD by E3 ubiquitin-ligases and the degradation of Notch [7]. This is necessary to avoid the persistence of Notch signaling which would lead to a gain-of-Notch function.

Although the four Notch receptors retain structural similarities, their function is not the same. Functional differences between the four Notch receptors are related to individual structural properties, to their temporal and cellular expression, to variations in the affinity of the Notch extracellular domain for its ligands and to differential interactions of the NICD with Rbpjκ [15,16]. For example, Notch1, 2 and 3 are expressed in bone, whereas Notch4 is slightly detectable in skeletal cells [17]. Notch3 is predominantly expressed in vascular cells, and as a consequence plays a key role in vascular development, and Notch4 is expressed in endothelial cells and plays a role in the development of vertebrate endothelium [18]. *Notch4* mRNA is detected in the endothelium of highly vascularized adult tissues, such as lungs, heart and kidney. Notch needs to interact with ligands present in neighboring cells of the same or different lineages for its activation, and Jagged1 is the prevalent ligand expressed by skeletal cells [19]. Notch1 and Notch2 are structurally similar, but either the *Notch1* or *Notch2* inactivation results in embryonic lethality, indicating that their functions are not redundant [20–22]. The structure of Notch3 diverges, and the amino acid identity of the Notch3 NICD is significantly different from that of Notch1 and 2 [23]. This, as well as a