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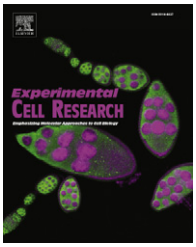

Review Article

Notch signaling in diabetic nephropathy

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ABSTRACT

Notch signaling is an evolutionarily conserved cell–cell signaling system that controls the fate of cells during development. In this review, we will summarize the literature that notch signaling during development controls nephron number and segmentation and therefore could influence kidney disease susceptibility. We will also review the evidence that Notch is reactivated in adult-onset diabetic kidney disease where it promotes the development of nephropathy including glomerulopathy, tubulointerstitial fibrosis and possibly arteriopathy and inflammation. Finally, we will review the evidence that blockade of pathogenic Notch signaling alters the natural history of diabetic nephropathy and thus could represent a novel therapeutic approach to the management of diabetic kidney disease.

Contents

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Introduction to diabetic kidney disease

Diabetes mellitus is complicated by nephropathy in approximately 35% of patients making diabetic kidney disease (DKD) the leading cause of end stage renal disease in the United States and in the developed world [1]. Poor glucose control and uncontrolled hypertension are important risk factors for the development of nephropathy; however, there also appears to be a genetic component to the disease as a family history of kidney disease is a strong predictor of renal functional decline [2,3]. Current therapy is aimed at improving glucose control and lowering intra-glomerular pressure by controlling systemic blood pressure preferably with renin–angiotensin system inhibitors. However, despite intensified glucose control and the widespread use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, the prevalence of diabetic nephropathy continues to increase [1] and new therapeutic strategies are urgently needed.

Diabetes affects many different cell types in the kidney. Traditionally DKD is considered to be part of the microvascular complications of diabetes mellitus, indicating the key role of the dysfunctional endothelial cells. Renal histology in DKD is characterized by thickening of the basement membrane, mesangial expansion and podocyte loss, indicating that all layers of the glomerular filtration barrier are involved [4]. Advanced DKD is also characterized by tubulo-interstitial fibrosis, accumulation of activated myofibroblasts, collagen and inflammatory cells and loss and dedifferentiation of tubular epithelial cells [4]. In this review, we will focus on the role of the Notch signaling pathway as a regulator of glomerular, tubular, vascular and immune functions during the development and pathogenesis of DKD.

Notch signaling; the basics

Mammalian Notch receptors (Notch1–4) are a family of ancient transmembrane proteins that are present in all metazoa and are key regulators of cellular development, differentiation, survival and function. Notch signaling is short distanced as it requires cell–cell contact when the extracellular domain of the Notch receptor engages a Notch ligand on an adjacent cell (Fig. 1). The active receptor then travels to the nucleus without a signal amplification step. The effects of receptor engagement are cell-type and context dependent. This is usually achieved by interacting with other signaling pathways including, but not limited to hypoxia inducible factor (HIF1) [5,6], transforming growth factor (TGF-β)/Smad [7], Wnt/β-catenin [8,9], NFκB [10] or vascular endothelial growth factor (VEGF) [11,12].

Notch receptors have a conserved domain structure (Fig. 1) [13]. The N-terminal Notch extracellular domain (NECD) consists of multiple epidermal growth factor (EGF) repeats and a highly coiled negative regulatory region containing the Notch/Lin domain (NLD) which is the hallmark of this receptor family. The single transmembrane region connects the NECD to the C-terminal Notch

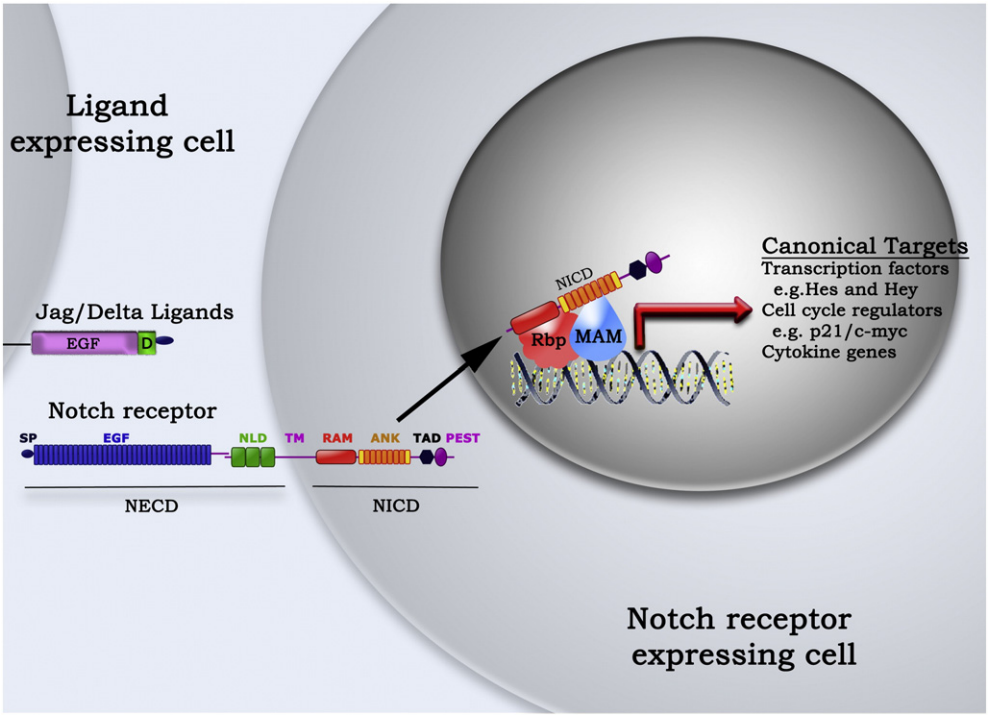

Fig. 1 – Schematic representation of Notch signaling. Notch signaling is initiated during cell–cell contact when a Notch receptor comes into contact which a jagged (Jag) or delta-like (delta) ligand. Ligand engagement releases the Notch intracellular domain (NICD), which translocates to the nucleus to initiate canonical or non-canonical signaling.ANK — ankyrin repeats, EGF — epidermal growth factor repeats, MAM — mastermind-like, Hes — hairy-enhancer of split, Hey — hairy/enhancer of split related with YRPW motif, NLD — Notch/Lin domain, PEST — proline (P), glutamic acid (E), serine (S) and threonine (T) sequence, RAM — Rbp-jκ associating motif, Rbpj — recombination signal binding protein for immunoglobulin kappa J, SP — signal peptide, TAD — transactivating domain, TM — transmembrane region.