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Notch signaling in pathogenesis of diseases

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Abstract

Multiple myeloma (MM) is an incurable plasma cell malignancy that affects predominantly older adults. Approximately 116,000 new cases are diagnosed annually worldwide. Progress has been made since the introduction of the first immunomodulatory drug and proteasome inhibitor for treating MM, but there are still several hurdles. There remains an unmet need for patients to be treated outside available clinical trials, in particular those elderly patients with at least one adverse prognostic factor. Monoclonal antibodies targeting CD38 or SLAMF7 combined with either a standard induction scheme or as part of a fixed combination with a proteasome inhibitor were approved by the regulatory agencies. The former demonstrated encouraging results in frail and elderly patients treated with bortezomib-sandwich schemes or subcutaneous daratumumab. New next-generation proteasome inhibitors with more favorable toxicity profiles or orally administered immunomodulatory drugs with alternative mechanisms of action are very likely to dramatically extend the therapeutic armamentarium window. There are still several hurdles that remain to be crossed, such as the treatment of patients who have no appropriate candidates for lenalidomide-based induction regimens due to early relapse or the inappropriate sequential use of anti-CD38 antibodies. Current staging systems for multiple myeloma have limitations, particularly for risk stratification. In addition to basic laboratory experiments on new compounds or drugs, animal models of myeloma are needed as they provide in vivo preclinical data that translate into the later clinical phases. Moreover, there is emerging interest and research in developing artificial intelligence-driven or algorithmic approaches to staging systems with integration of multiple omics data. Current treatment options for newly diagnosed, untreated, and transplant-ineligible multiple myeloma patients have become increasingly sophisticated, patient-tailored, and require implementation of novel patient care organizational models. Treatment algorithms involve patient-specific selection of a particular induction combination chemotherapy scheme and defining the ideal timing for subsequent treatment intensification versus maintenance therapy options.

Keywords: Notch; Pathogenesis; Cancer; Signaling pathway; Crude odds ratio

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Introduction

Proper development and homeostasis of metazoans require precise control at multiple levels of gene regulation. Transmembrane Notch receptors, Notch ligands, and the Notch pathway components comprise Notch signaling, which is a highly conserved signaling system characterized by an array of cellular and systemic functions participating in the development and homeostasis of metazoans. Mastering Notch plays a vital role in morphogenesis during embryo development by regulating cell proliferation and differentiation. In our cells, different organs express distinct sets of Notch receptors and Notch ligands; cells expressing the Notch receptor can either be adjacent to a signal-receiving cell or co-express the Delta and Serrate families of the Notch ligand. Sufficient Notch ligand can bind and activate the Notch receptor in signal-receiving cells. Activated Notch receptor comprises features of proteolysis, release of a Notch intracellular domain, and transmigration from the plasma membrane to the nucleus. We classify all identified Notch signal pathway components to include Notch receptor, Notch ligand, Notch transcriptional complex, signal transducer, and cellularization. Distinct cells can interact and trans-activate Notch signaling in the Notch pathway for signal transduction and regulation of the different target genes. Moreover, Notch signaling activation and Notch ligand-induced endocytosis play critical roles in Notch function for proper signal transduction, and Notch trafficking is critical for the destiny of Notch. Notch signaling crosstalks with several key signaling pathways. Dysregulation of the Notch signaling pathway can lead to divergent diseases, such as cancer and leukemia, Alzheimer's disease, CADASIL, and diabetic complications.

2. Notch Signaling Pathway Components

Notch signaling is a highly conserved pathway that is essential for the determination of cell fate and regulates the cell fate decision in various processes of development. The outcomes of Notch signaling are diverse and depend on the context of ligands, the presence of other signaling pathways, and levels of Notch signaling. Notch is involved in numerous cellular processes and frequently plays an important role in disease development. In this review, we focus on some recent developments related to the involvement and potential implications of Notch signal components in various human diseases.

Notch Receptor Components Briefly, ligand-mediated activation of Notch signaling involves the movement of the Notch intracellular domain into the nucleus, where it then modulates the transcription of target genes. In humans, four Notch receptors and five ligands have been identified. The transcription-regulation complex is composed of RBPJ, NICD, Mastermind-like proteins, histone acetyltransferase p300, and histone deacetylase. In the absence of mature Notch receptors, RBPJ binds to co-repressors, which suppress the transcription of Notch target genes. When a Notch receptor-containing ligand binds to the Notch receptor, the Notch receptor is cleaved into NICD by two cleavage events. The NICD translocates to the nucleus,

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where it binds to the transcriptional activation complex and activates Notch target genes. To achieve this mission, we believe it is essential to obtain a better understanding of the Notch signaling pathway. In this review, we focus on some of the recent developments related to the involvement and potential implications of Notch signal components in various human diseases.

Notch Receptors

Notch receptors are single-pass type 1 transmembrane proteins that exist as heterodimers. The extracellular domain contains several epidermal growth factor like repeats. A notable feature of Notch proteins is their proteasomal cleavage via furin convertase, which occurs in the trans-Golgi network during anterograde transport of Notch polypeptide. This cleavage results in the production of a noncovalently associated heterodimer consisting of an extracellular domain plus a transmembrane subunit. The Notch extracellular truncation region differs between different Notch isotypes. Following synthesis, the Notch dispensable signal subunit locally associates with the Notch transmembrane subunit, which contains the conserved heterodimerization domain. This association may promote proper processing of the Notch molecule; deletion makes Notch dispensable in some developmental conditions. Upon ligand binding, the Notch transmembrane subunit undergoes an additional proteolytic cleavage followed by a γ-secretase-mediated intramembrane cleavage within the transmembrane domain, which results in the release of the intracellular domain from the plasma membrane and its translocation into the nucleus. In the nucleus, Notch binds to the DNA-binding protein. This binding allows the NICD to shed transcription corepressors and to recruit transcription coactivators, which leads to the activation of Notch target genes.

2.2. Ligands

Delta-like proteins (DLL1, DLL3, and DLL4) are the main ligands that bind to Notch receptors. The interaction of Jagged ligand proteins (JAG1 and JAG2) with the Notch receptors has been previously described. The binding of Notch receptors (NOTCH1, NOTCH2, NOTCH3, and NOTCH4) to these ligands results in proteolytic cleavage of Notch and liberation of the Notch intracellular domain (NICD), which then translocates to the nucleus where it functions as a transcription factor. It has been reported that JAG1 induces Notch-regulated cytokine production in Th17 cells by binding to NOTCH1 on the Th17 cells. Furthermore, JAG1 expression is positively correlated with the levels of IL-6, IL-17, and IL-22 in RA synovial tissue. DLL4 blockade inhibits Th17 cells in vitro, and Notch signaling-activated IL-6 promotes Th17 cell differentiation in PsA. In summary, the Notch ligands JAG1 and DLL4 start Notch signaling and activate Notch signaling by binding to Notch receptors NOTCH1 and NOTCH2.

JAG1, encoded by the gene JAG1, is one of these ligand proteins and is one of the two ligands reported to induce Th17 cells. Previous studies have shown that Notch ligands JAG1, DLL1, and DLL4 are expressed in human synovial tissues. The Notch1 ligand JAG1 is expressed in

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the blood of the C578L mouse model of AIA, and the expression of JAG1 is significantly higher in the plasma of pristane-treated SLE mice than in the control mice. JAG1 activated Notch signaling by binding to the Notch1 receptor and was essential for the induction of Th17 cells. These studies prompted us to investigate the expression of JAG1 in spondyloarthropathy and the function of JAG1 in Th17 cells.

Downstream Effectors

In mammals, the Notch signaling pathway consists of four receptors and five ligands. The binding of ligand to the Notch receptor leads to proteolytic cleavages and the release of the Notch intracellular domain. NICD translocates into the nucleus and forms a transcriptional activation complex with different coactivators, converting the key downstream target genes into active transcription forms. In general, target genes include hairy/enhancer of split and HES-related repressor proteins. These Notch signaling target genes are involved in distinct cellular processes, such as differentiation, proliferation, apoptosis, and fate determination.

Several factors may cross-talk with Notch signaling. For instance, Notch signaling may antagonize the p53-dependent apoptosis and tumor-suppressive pathways by the combination of HES and HERP stability. Notch could interact with p53, or the activation of HES and HERP can be repressed by p53. p53 antagonizes Notch signaling downstream events in the outcome formation of the cell. In osteogenic differentiation, p53 represses the transactivation of NICD. However, in the circumstances of DNA damage, the p53 level is elevated; nuclear MDM2-bound p53 can combine with NICD and promote the phosphorylation and acetylation of NICD for proteolysis-dependent degradation. Notch signaling can also reduce p53 expression. Heterogeneous nuclear ribonucleoprotein is an oncoprotein in cancer development, and it enhances Notch expression by post-transcriptional modifications. However, the combination of Notch signaling and hnRNP K inhibits the function of p53; as reported, hnRNP K impairs p53-dependent reactions and strengthens the ability of Notch-induced oncogene-driven tumor development. The feedback mechanism in Notch signaling is complicated; we still have much to learn from it before we can use the dominant side, manipulation, to inhibit tumor progression or to enhance tissue development after chemotherapy.

Regulation of Notch Signaling

The ability of the Notch pathway to evoke its responses is regulated at multiple levels. In mammalian cells, Notch signaling is regulated at the levels of Notch ligands and receptors, the secretase-mediated release of NICD, the nuclear import of NICD, and its transcriptional activity. Notch signaling is an extremely short-lived event from signal induction to NICD-driven transcriptional responses. This affords a very tight regulation of cellular differentiation. Impaired regulation may result either in Notch signaling hyperactivity, which is associated with cancers, or Notch signaling hypoactivity, which results in developmental defects including cardiovascular

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and neurodegenerative diseases and cancer. Both gain- and loss-of-function mutations affect essential constituents of the Notch signaling pathways. In mammals, the pathways contain four Notch receptors and five Delta and Serrate ligands. Here, we summarize the regulation of Notch signal transmission from the induction of the ligands, through signal transduction, to the nuclear activities of Notch in the nucleus. Moreover, we provide an overview of the effects of the signaling modulators discovered thus far, including aspects of Notch signaling regulation that are specific to the different mammalian cells, such as embryonic stem cells, myogenesis, oligodendrocyte and muscle development, as well as pathological situations.

Regulation of Notch Signaling

Notch signaling pathway plays critically important roles at distinct developmental stages. Notch signaling involves multiple regulation steps. Upon ligand engagement, Notch receptors are cleaved to release NICD to act as a transcription cofactor. This process requires sequential proteolysis by members of the A Disintegrin and Metalloprotease and γ-secretase protease families. To prevent sustained activation of this pathway, several proteins shape a regulatory network to fine-tune either Notch receptor or signaling. Normally, Notch receptors are ubiquitinated, endocytosed, and delivered to the lysosome for degradation. Ubiquitination is not only required for Notch clearance but also acts as a switch for sorting activated Notch to the endosome for degradation after ligand binding. FBXW7 is a known E3 ligase for this receptor. Although there are reports indicating this F-box protein also targets Notch for degradation, the results are contradictory.

Ligand endocytosis is important to down-regulate Notch signaling. In the absence of ligand, Notch receptors undergo endocytosis for constitutive turnover. The mode of Notch endocytosis varies in different cell types. At least two adaptors, endocytic protein Numb and Epsin, for NICD were reported. Numb is also an essential negative regulator of Notch signaling in multiple settings. Numb and Numb-like, two evolutionarily conserved proteins, are reported to be SBDO proteins that can directly reduce the output and propagation of Notch signaling. Numb promotes Itch-dependent ubiquitination of Deltex to control Notch activity in Drosophila. Numb also binds to Notch directly and targets the NICD with Alteration/Defective 1 for ubiquitination-dependent degradation. Epsin is reported to be SBDO proteins that interact with Paired box domain protein PPxY motifs to recognize the YxNPxY motif in the intracellular domain of mammalian Notch. The interaction between endocytic proteins and Notch following Notch binding to ligand during tandem endocytosis was characterized. Numb must be present on the endosomes to trigger Notch into the productive degradation path.

Notch Signaling in Development

The Notch signaling pathway is highly conserved in evolution and has been shown to be required for normal development and tissue homeostasis in many organisms. Several early

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studies that addressed the actions of Notch and the interaction of Notch and developing tissues provide important insights. It has been evolutionarily conserved and is used reiteratively in a multitude of developmental processes. Bizarrely, the requirement for Notch signaling at prescribed time points during development is often strikingly conserved, for example in the establishment of metameric arrays of somites by segmental mesoderm, the 'decisions' driving maturation of pre-T cells to goblet cells in the intestinal epithelium, and endocrine specification of the ventral neural tube. Embryological analysis led to a simple and elegant model of Notch signaling that has been tested repeatedly. Notch signaling can activate or repress transcription. In most contexts, interactions between cells expressing Notch ligands and cells expressing Notch receptors are juxtacrine, and can also be transduced by the Delta and Serrate homologues of Notch found in Drosophila in transgenically reconstituted embryos. The putative roles of these regulators were deduced by asking to what extent the reported alterations in developing tissues reflected primary effects, and by comparing the phenotypes to the signaling activity of Notch in cell culture.

Notch Signaling in Cancer

Many different reports have described an activation of Notch signaling in a number of cancer forms, both in solid and hematological tumors. The data about the role of Notch signaling in cancer are ambivalent; i.e., depending on the tumor, there are reports that show an activation of Notch signaling and progression of the tumor, while others show a suppression of the tumor. The publication of certain researchers was one of the first that described the aberrant Notch signaling in cancer, and since then a lot of research on this subject has been performed. Complicating the interpretation of data about the role of Notch signaling in cancer was the discovery of several pathways with which Notch could interact. The role of some of these pathways in carcinogenesis is already well known, and others are being studied. Ongoing work has disclosed a number of differences in the response of Notch pathway inhibitors between Notch-dependent and Notch-independent cancers, which certainly need to be taken into account in the selection of the patient population for therapy.

Cancer stem cells are a small subpopulation of the cells within a tumor, but they are believed to be responsible for the growth of a tumor and resistance to therapies. The study connected with the development of cancer stem cells as new targets for novel therapies is now a growing topic, and significant progress has been made. A relationship between Notch signaling and cancer stem cells has been described by several independent groups. An involvement of Notch signaling in the development of carcinoma of the cervix, pancreas, tumors of the liver, prostate, pituitary gland, colon, skin, and others has been shown. The ability to regulate the proliferation and differentiation of normal tissue stem cells, and often stem cells of hematopoietic origin in mice, has also been described. Recently, reports about the role of Notch signaling in the

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maintenance of cancer stem cell function and their activity in tumors have been published, and this has been confirmed in patients.

Role in Tumor Initiation

Notch was originally identified from chromosomal breakpoints in T-cell acute lymphoblastic leukemia. We have witnessed a huge volume of data supporting its active role in tumor progression. Notch is required for the initiation of T-ALL in several distinct in vivo models and yields CD4+CD8+ T-cell leukemia after a long latent period. Inhibition of the Notch pathway reduced the ability of T-ALL cells for establishment and propagation. Overexpression of Notch1 from the recombinant viral vector can induce multi-stage mammary tumors. Besides Notch1, the expression of Notch3 also promotes mammary tumor development in the mouse models for breast cancer. Expression of an activating Int-3 Notch allele induced ovarian tumors in mice, and the non-activating Int-3 allele retarded papillomagenesis.

Interestingly, there was no statistical difference in overall tumor onset and tumor incidence between the compound mutants. The presence of the mammary stem cells was not affected by the compound mutation. However, the compound mice had a longer tumor latency in secondary recipients, suggesting that Lfng and Notch4 were involved in the postnatal development of mammary tumors by regulation of asymmetric division. Among the Notch family members, Notch3 has been demonstrated to be tumor-related in ovarian carcinoma. The importance of Jag1 and Delta1 in mammary stem cell biology was demonstrated through the incorporation of membrane-bound EGFP into mouse strains carrying a mutant ligand allele.

Role in Tumor Progression

Angiogenesis is essential for the growth, proliferation, and invasion of tumors, playing a central role in the development of cancer and in determining the metastatic ability of tumors. Notch signaling is also involved in tumor angiogenesis formation and blood vessel maturation, and all five Notch ligands and two Notch receptors often play opposing roles under different conditions. The Notch pathway can help improve the hypoxic microenvironment of tumors by stabilizing the expression of hypoxia-inducible factors under hypoxic conditions or through transcriptional crosstalk with the hypoxia-inducible factors, thus improving the tolerance and survival of breast cancer cells. In addition, Notch signaling is associated with invasion and metastasis in a variety of tumor types, such as lung adenocarcinomas, where Notch influences the invasive capability of lung cancer cells. The TGF-β pathway affects a variety of cellular processes in pancreatic cancer, including signaling within cancer cells and between cells and their stroma.

Some Notch target genes, including connective tissue growth factor, c-Myc, IL-6, and NF-kB, have been revealed and shown to contribute to tumor-stromal interaction and the proliferation and survival of cancer cells, while other Notch target genes turned out to be involved in the

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inhibition of cancer-stromal interaction and tumor proliferation and survival. Additionally, a portion of the Notch ligands is reportedly involved in tumor progression, or more accurately, in immunosuppressive signaling that allows tumors to avoid immune surveillance. Indeed, the next generation of therapeutic strategies includes the use of monoclonal antibodies that disrupt the malignant signaling between Notch ligands and the immune system. The different functions of Notch signaling in various tumors might be dependent on its specific ligand/receptor, cellular context, or intradomic interactions. It is also complex and has different roles dependent on the tumor type and stage, indicating the dual effects of the Notch pathway in cancer.

Therapeutic Targeting

One of the primary goals of understanding the pathogenesis of life-threatening diseases is to translate acquired knowledge into new diagnostic tools and therapeutic avenues. Although gamma-secretase has been the target of gamma-secretase underpinning the rationale, a big concern for developing such drugs is compensating side effects of long-term therapy. Nonetheless, blocking the interaction between CSL and recruited coactivators Mastermind or histone acetyltransferases may provide a valid therapy because such coactivators are not typically employed by CSL-bound repressors. More importantly, not all Notch target genes require sequence-specific DNA binding by CSL for regulation. In this case, it is possible that a CSL-independent Notch signaling pathway could be subject to gene side effects of the gamma-secretase inhibitor family of drugs or patients with gain-of-function Notch mutations.

Several lines of evidence underscore a mechanistic connection between Notch mutations and apolipoprotein E and LDL receptor-mediated hypercholesterolemia. These observations offer the potential to think about Notch as a target for the treatment of heart and vascular diseases, from the perspectives of understanding the mechanisms of developmental programming of human heart disease and from the development of effective new strategies to prevent or slow it. A more recent study with Notch1 antisense oligonucleotides in LDLR mice showed that inhibiting Notch1 protein synthesis also reduces the induced expression of the atherosclerotic disease marker, vascular cell adhesion molecule-1. Collectively, these studies establish Notch signaling as a potential therapeutic target for heart or vascular disease and suggest strategies for developing novel agents that could be employed for this purpose.

Notch Signaling in Cardiovascular Diseases

Notch receptors regulate cell fate decisions by controlling various cellular processes from development to tissue homeostasis and angiogenesis. Accumulated evidence has revealed the roles of Notch signaling in the development of the cardiovascular system and in modulating cardiovascular diseases. In this section, we will focus on Notch signaling in cardiovascular diseases, including heart and vascular structure and genetic diseases.

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Cardiomyocytes communicate with their extracellular matrix during development and throughout life. By this means, cardiac muscle integrates each single function into an orchestrated wall motion of the entire heart. It is now well appreciated that the extracellular matrix plays a crucial role in mediating essential intercellular potentials for cardiomyocytes and their activity responses. The Notch signaling pathway in different cellular players of the myocardium is intimately involved in the formation of the complex cardiac conduction system. Impairment of both ion channels and intercellular coupling might have an additional important consequence: an increased risk of ventricular arrhythmia. Rather than reducing heart size in the long term, low expression of Jagged1 seems to be beneficial for mechanical function by reducing the end-diastolic pressure-volume relations, possibly by reducing the associated massive switch from a mature cardiac muscle contractile gene expression program to a 'fetal' contractile gene expression program.

Notch Signaling in Neurological Disorders

Notch signaling is evolutionarily conserved and plays a vital role in various developmental processes such as cell fate determination, differentiation, proliferation, and apoptosis. Increasing evidence suggests that deregulated Notch signaling contributes to the initiation, progression, and poor prognosis of several diseases, including cancer, neurological disorders, cardiovascular diseases, and immune system disorders. The involvement of Notch signaling either in alleviation or aggravation of several diseases denotes its paradoxical role. Hence, agents suppressing or activating Notch signaling could be used for the alleviation of several diseases. In this systematic review, we focus on the role of Notch signaling in neurological disorders.

Many of our body functions depend on our neurological system, which includes our brain, spinal cord, and many neurons connecting the spinal cord and brain to several tissues. These poorly regenerating neurons are extremely sensitive to various genetic or environmental harming stimuli. Genetic mutations, inflammation due to infection, trauma due to injury, or toxicity associated with many chemicals can contribute to the development of neurological diseases. Several biological processes like cell differentiation, proliferation, growth, and self-renewal mediated by Notch signaling are critical for the development and maintenance of the nervous system. The association between Notch signaling and nervous system-associated diseases, including Alzheimer's disease, developmental malformation, cancer, traumatic brain injury, some specific types of inherited vacuolar disorder, multiple sclerosis, pediatric glioma, temporal lobe epilepsy, cancer, and neuropathy-related diseases like Charcot-Marie-Tooth disease, vestibular schwannoma, and Parkinson's disease-mediated dopaminergic neurons, were reported. Despite its controversial role, researchers are still enthusiastic about modulating the Notch signaling pathway as a promising therapeutic strategy for many neurological diseases.

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In this review, we aim to consolidate this concept and make basic and clinical researchers more aware of Notch's intricacies as potential targets.

Notch Signaling in Immune System Disorders

Notch signaling has vital roles in T cell commitment, development, and differentiation, and is involved in T cell activation, interleukin-17 production, regulatory T cell differentiation, and the function of thymic dendritic cells. Additionally, Notch signaling is crucial for the development of invariant natural killer T cells and tissue-resident memory T cells. Furthermore, emerging evidence indicates that Notch signaling is implicated in T cell memory and immune surveillance in peripheral tissues. Notch signaling also functions in lineage specification and activation of the myeloid lineage, including thymic dendritic cells, mononuclear phagocytes, neutrophil precursors, macrophages, and distinct dendritic cell subsets. Moreover, Notch signaling is involved in the networks that regulate class-switch recombination to facilitate effective B-lymphocyte activation during T cell-dependent humoral immune responses. The majority of Myc-driven T-ALL mouse models require the acquisition of cooperating mutations that involve Notch1 signaling to promote leukemia development, and T-ALL may occur from transformation through Myc overexpression; it may develop from early prenatal transformation that is associated with robust Notch activity. Dysregulated RBPJκ-Notch signaling also promotes cancer stem cell properties and contributes to the development of AML. Some cancers and HIV infection are enhanced by dysregulated Notch signaling, although the underlying mechanisms remain to be discovered. Furthermore, earlier data indicated that Notch signaling may be a therapeutic target for autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus.

In the last few years, there has been considerable progress in understanding the regulation and function of Notch signaling in adaptive and innate immune responses, and by discussing Notch-related research in the immune system from the past two years, we hope to provide important insights that will guide future research. A thorough understanding of the role of Notch signaling in shaping the immune system is critical for our ultimate goal of exploiting this knowledge to benefit human health. In particular, further dissecting the functions of Notch signaling in the immune system has implications for cancer therapy and immune system disorders, and progress in this field could also lead to the design of new immune intervention strategies. More knowledge is needed about how different Notch pathway components control both general Notch function and specific immune outcomes. With our increasing understanding of the contribution of Notch signaling to human health and disease, rational strategies for targeting Notch pathway components and modulating Notch activity in disease states are both possible. Notch signaling plays crucial and diverse roles in different types of immune cells during cellular differentiation, cellular fate decisions, and immune responses, and dysregulated Notch signaling may contribute to immune system disorders such as autoimmune diseases, lymphoid

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malignancies, and aggravated HIV infection. Additionally, anatomical and time point-specific Notch-blockade strategies for T-ALL treatment have demonstrated promising results. However, many problems remain to be solved in the clinical development of Notch signaling blockers that specifically treat immune system disorders, and the best approach is to simultaneously control activated Notch and suppress ligand-induced hyperactivation in diverse tissues and periods.

Notch Signaling in Metabolic Diseases

Notch is a signaling receptor in noncanonical Wnt and noncanonical EGF growth factor pathways and plays important roles in metabolism, including gluconeogenesis, insulin resistance, and obesity. Notch plays opposite roles in gluconeogenesis, predominantly induced by the Notch2/Herp axis, while NCor1 confers a direct inhibitory effect on gluconeogenesis. In the fasting state, skeletal muscle-derived Fstl1 triggers β-adrenergic-dependent fatty acid oxidation in the liver as a systemic metabolic checkpoint. Notch1 is associated with NCor1 to inhibit the activity of the gluconeogenic enzymes Pck1 and G6pase in response to Fstl1. Moreover, Fstl1 activates the Notch/Fos axis to enhance the expression of mitochondrial compartment proteins. In glucose-induced metabolic psychiatric disorders, Notch forms a repressive complex with Ncor1 to inhibit the stabilization of the β-cell mass and to generate β-cell insulin resistance, while Erk, Mafa, Rgs16, and Tcf7l2 function to confer a permissive context. When Notch signaling is downregulated, β-cell function could recover. In obesity-related metainflammatory hepatic diseases, circulating proteoglycan SDC1 activates the Notch1 pathway in a domain-dependent manner. Notch1 is critical for SDC1-driven upregulation of the EMT-related markers Snail, Twist, and TGFβ. However, Notch1 could be controlled pharmacologically by targeting drugs. Co-treating with these Notch-targeting drugs alleviates hepatic steatosis and liver injury.

10. Notch Signaling in Inflammatory Diseases

Inflammatory diseases occur in the vasculature, lung, or sepsis, manifested as systemic inflammation, organ dysfunction, shock, and multi-organ failure. In these diseases, the pro-inflammatory cytokines or chemokines are systemically or uncontrollably induced, leading to the inflammation of vascularity or immune cells. The regulation of pro-inflammatory molecules in these cells needs to be highly regulated and strictly controlled because the overexpression of pro-inflammatory molecules exerts detrimental effects, accelerated by systemic inflammation, shock, and multi-organ failure. Genetic deletion or pharmacological blockade of Notch suppresses inflammatory stimulation and injury, leading to the downregulation of pro-inflammatory molecules and inflammatory cells. Blockade of Notch signaling attenuates pulmonary inflammation and tissue damage. The studies deliver significant implications by showing that the regulation of Notch signaling may have therapeutic benefits. The overexpression of pro-inflammatory molecules and infiltration of inflammatory cells can be stimulated by pathogen-associated molecular patterns. Inhibition of Notch signaling attenuates

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the effect on tissue structure. In this study, the expression of inflammatory cytokines in lung tissues was significantly elevated following administration, and inhibition of Notch resulted in downregulated expression levels. In conclusion, the above studies have shown that activation of Notch signaling can potentially engage in the induction of inflammation, promotion of injury, and increased expression of pro-inflammatory molecules. The findings from these studies underline the role of Notch signaling in the pathogenesis of inflammatory diseases, including systemic inflammation, organ dysfunction, shock, and multi-organ failure. Therefore, pharmacological modulation of Notch pathways may open new perspectives for designing and developing innovative therapeutic strategies targeting inflammatory diseases.

Notch Signaling in Genetic Disorders

Alagille syndrome (AGS) is a rare monogenic disorder that primarily affects the liver, heart, skeleton, eye, face, and skin. The syndromic aspects of AGS are attributed to the paucity or absence of medium- to large-sized bile ducts in the liver, which in turn leads to chronic cholestasis. Defective bile duct formation during biliary development can be attributed to haploinsufficiency of JAG1 in 94% of cases. Over the last decade, advances in human genomics have unexpectedly revealed that several other unrelated genetic disorders are also caused by pathogenic mutations involving different components of the Notch signaling pathway. The majority of these conditions exhibit distinctly different phenotypes to AGS, of which some also occur independently of JAG1. Unsurprisingly, many recent reviews have been published on AGS, which now extend beyond pediatric/internal medicine and cover diverse aspects of the JAG1/Notch signaling pathway emanating from different organs.

The present review focuses instead on the consequences of Notch2-induced disease pathology affecting various organs. In addition to AGS, studies on Jag1/Notch2 null, liver-specific Cre recombinase knockout mice revealed that Jag1/Notch2 pathway perturbation can also result in intrahepatic cholestasis and bile duct paucity. Due to negative in vivo findings in adult mouse liver, attention later focused on organs outside the pediatric physiological window of WNT, BMP, and Notch-induced canonical cholangiocyte formation. The vast majority of Notch2-ICD disease pathology becomes apparent only after embryonic cholangiocyte specification periods between embryonic day 14.5 and 17.5 in the skin/hair rich areas of the dorsum and tail. Preliminary findings, however, indicate that Notch signaling involvement can also occur at other time points in other tissues/organs beyond the pediatric window.

Notch Signaling in Stem Cell Biology

Notch signaling is crucial for tissue homeostasis by maintaining a balance between quiescence, self-renewal, and differentiation in many tissues, including neuroprogenitors, hematopoietic, and gut stem cells in the adult. The Notch pathway prevents differentiation in stem cells and instead promotes the renewal of the stem-like state. In most instances, Notch prevents

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progenitor differentiation and maintains stem cell self-renewal by repressing the expression of tissue-specific transcription factors through activation of the Hairy Enhancer of Split (HES)-type family of basic helix-loop-helix (bHLH) proteins in the cell nucleus. The major effectors of Notch receptor activation are the transcriptional repressors, HES1 and HES5. The protein product of HES1 represses pathways controlled by Neurogenin1 and Pax6, two determinants of maturation toward the neuronal lineage. In recent years, it has been possible to establish primary neural stem and progenitor cell culture conditions and to manipulate the intrinsic signaling pathways regulating stemness and differentiation. Similarly, it is possible to manipulate crypt stem cell stemness and differentiation phenotype.

Although cancer stem cells account for a very small percentage of tumor-initiating cells, they are considered to be a putative cause of chemotherapeutic resistance and relapse due to their self-renewal and differentiation capabilities. Notch signaling is known to control stem cell self-renewal and differentiation in normal tissues, as described earlier. Indeed, the aberrant activation of Notch signaling has been identified in a variety of neoplastic human diseases, and cancer stem cells displaying overexpression of activated Notch1 were identified in a number of solid tumors. In several stem cell studies, substantial evidence has been made to suggest that different cancers originate from different normal stem cell types: breast cancer from mammary stem cells, brain tumors from neural stem cells, prostate cancer from prostate stem cells, and leukemia from hematopoietic stem cells. The Notch pathway is furthermore implicated in many cancers, and it is known to be associated with the maintenance and survival of several cancer stem cells.

Notch Signaling in Tissue Regeneration

To successfully replace another damaged or diseased tissue, the differentiation process of stem cells or progenitors needs to be highly controlled and properly coordinated with the signals delivered from surrounding tissues via various signal transduction pathways, such as kinase-mediated signaling and Notch signaling. Both stem cells and progenitors are regulated by the stem cell niche, which provides a microenvironment that maintains stemness or restricts their differentiation. Under the proper signaling environment of the niche, stem cells and progenitors may undergo active self-renewal and differentiation when needed during the regeneration process. The Notch signaling pathway is considered a central pathway for cell-cell communication that plays a critical role in maintaining tissue homeostasis during regeneration throughout adulthood. Notch signaling plays an essential role in postnatal tissue repair and regeneration. Thus, Notch signaling has been found to regulate tissue-resident stem cells and progenitor cells, epidermis repair, skeletal muscle regeneration, tooth regeneration, hair cell regeneration, liver regeneration, and regulating regeneration after injury in several other tissues.

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In many tissues, adult stem cells and progenitor cells seem to exclusively reside in a specialized microenvironment known as the stem cell niche. The niche environment provides proper signaling to control the behavior of tissue-specific adult stem cells or progenitor cells. The signals from the stem cell niche continuously repress the cells from differentiating and ensure that the stem cells undergo self-renewal. Upon tissue injury or physiological demand, tissue stem cells may have to respond rapidly to replace the damaged cell types through differentiation and self-renewal to maintain tissue homeostasis. The gene expression and epigenetic regulation of stem cells can be quickly updated to adapt to the environment of tissue injury. The most studied adult stem cell and their well-known signaling niche components are Lgr5+ cells in small intestinal crypts. Recently, several reports have revealed that the activation of the Notch signaling pathway mainly occurs in the Paneth cells, thereby showing its importance in increasing the Lgr5+ cells and amplifying the secretory progenitor cells of the crypt. The dynamics of cells and genes during tissue regeneration of Notch signaling can provide opportunities for therapeutic strategies following tissue-specific progenitors or pathological processes.

Notch Signaling in Aging and Age-Related Diseases

Aging is a multifactorial process that is affected by multiple genetic and environmental factors. Genome instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, increased inflammation, and altered intercellular communication are considered "hallmarks of aging" and may contribute to the aging process. Aging enhances the risk of various diseases, such as type 2 diabetes, osteoporosis, Alzheimer's disease, and cancers. Among them, cardiovascular disorder-related diseases, or heart diseases, have been recognized as the major cause of morbidity and mortality, and current research has focused on identifying the relationships between Notch signaling and age-related cellular dysfunction, which can be associated with age-related cardiovascular diseases.

Multiple studies have shown that Notch signaling is activated or upregulated during aging and may exert both positive and negative effects on age-related cellular dysfunction. This concept is also supported by the fact that the lifespan is shortened after neuronal knockdown of the notch gene, while the overall lifespan is prolonged by suppressing Notch signaling. However, since the visceral muscles with enhanced Notch activity show increased contraction function, the specific functions of Notch signaling in the aging process of heart tissues need further investigation.

Notch Signaling in Infectious Diseases

Infectious diseases caused by pathogenic viruses, bacteria, fungi, and protozoa are a major public health issue. Notch signaling has been reported to regulate the development,

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differentiation, and function of both innate and adaptive immune cells. In this chapter, we review the advances made in our understanding of how Notch signaling is regulated and how it impacts immunity in the context of infectious diseases. In particular, we focus on recent insights into the different roles of Notch signaling in the highly organized processes involved in regulating the immune response by cell–cell contact. Infectious diseases constitute a serious public health issue. These common and serious problems can be caused by pathogenic viruses, bacteria, fungi, and protozoa. The host response to pathogens is a well-coordinated series of events, ranging from the detection of microbial products by a limited number of germline-encoded pattern recognition receptors to the effector mechanisms that fulfill the host's mission to control, clear, or kill the pathogen by using both the innate and the adaptive arms of the immune response. Notch signaling plays an essential role in the development, differentiation, and function of both innate and adaptive immunity.

Notch Signaling in Autoimmune Diseases

Although Notch signaling was classically considered exclusive for development and in cancer, recent advances demonstrate a critical role for Notch signaling in numerous inflammatory conditions, including numerous autoimmune diseases. Notch signaling is a major driver and modifier during the development and progression of inflammatory and pathogenic processes that are closely associated with cell stress. This is in line with the role of Notch in development, where signaling serves to generate and select cells in often competitive and injury-associated conditions, ranging from hypoxia to nutrient limitation. In fact, the core stress response pathways often target crosstalk points with Notch signaling. In this sense, it is not so surprising that Notch signaling acts as a modifier during inflammation and in autoimmune diseases, many of which are closely intertwined with cell stress.

For the diseases listed and discussed in the following text, cues associated with the disease trigger canonical and noncanonical Notch signals through four receptors, Notch1 to Notch4, and cell-specific ligands Delta-like 1, 3, 4, and Jagged 1 and 2. In individual disease settings, these signals influence preferentially T-helper (TH) cell differentiation or function, in particular TH1, TH17, and T regulatory cells (Tregs), and proinflammatory and immunomodulating mediators, such as nuclear factor-κB, cytokines, chemokines, interleukin receptors, selective integrins, and matrix metalloproteinases. This is in line with the dominant role of Notch as a signaling entity that influences gene regulatory networks.

Data collection also indicates that noncanonical Notch signals become predominant during inflammation and autoimmune diseases. In particular, noncanonical Notch crosstalk with hypoxia-inducible factor signaling influences effector TH cells, the outcome of effector cell reprogramming in the diseased tissue, and mediators and processes associated with nonclassic proinflammatory and immunomodulatory functions. These events are driven by gene network modification and target mainly select TH1 and TH17 cells; new subsets, such as

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microbiome-associated TH17 cells, are controlled by noncanonical Notch signals, while TH2 and T helper cell type 2 negative regulation, development, and activity are influenced through Notch activation of canonical signals. These Notch functions are not exclusive for immune cells since noncanonical Notch signals modify additional contributors to autoimmune diseases, such as inflammation, type 1 diabetes mellitus, and Aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorder that change the balance of the disease. Importantly, interactions between Notch and additional signaling molecules play privileged proinflammatory and immunomodulating functions activated in distinct autoimmune diseases.

Notch Signaling in Hematological Disorders

Given the role of Notch signaling involved in various hematological processes, it is not surprising that deregulation of the Notch pathway is commonly implicated in hematological malignancies. As Notch signaling is involved in proliferation, suppression of apoptosis, differentiation, and survival of hematopoietic stem and progenitor cells, dysregulation can have important effects on hematopoiesis. Notch1 is one of the four highly recurrently mutated genes in T cell acute lymphoblastic leukemia, a disease derived from T cell progenitors. Chemically induced loss or gain of function mutations of Notch1, Ras, and Pten in mice can induce the development of T-ALL, suggesting that dysregulation of Notch1 alone may not be sufficient in vivo.

Inhibition of Notch during T cell development leads to a variety of outcomes including successful T cell development, but with limited differentiation potential. Additionally, inhibition of Notch signaling can lead to accumulation of the stem and progenitor cells, leading to a lack of more differentiated cell types. In addition to T-ALL, Notch signaling has been found to play a role in several other hematological malignancies, and the development of inhibitors was prompted following the identification of a translocation resulting in the activation of Notch2 in cases of marginal zone B cell lymphoma. Indeed, circulating Notch1IC was found to be able to reprogram early thymocytes or LSKs into T-ALL or Pre-T cells. In summary, Notch signaling can lead to T-ALL, but upon inhibition, it can also have a large influence on other stem and progenitor cell populations.

Notch Signaling Crosstalk with Other Signaling Pathways

Notch signaling could cross-talk with other signaling pathways, and this crosstalk acts as a regulatory node where signals from the different pathways converge, and output regulation is determined. The number of Notch crosstalk events provides mechanistic links between Notch signaling and other signaling activities. Most of the other signaling pathways that Notch signaling crosstalks with are in the framework of the activation of Notch-dependent target genes together with the signaling pathways, such as hedgehog, Wnt/beta-catenin, nuclear factor-kappaB, and Ras/Raf/mitogen-activated protein kinase. Also, some studies may focus on

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regulated feedback on protein levels and possible actions to crosstalk with Notch signaling in development and tumorigenesis, such as p53, Rap1, and Ras.

The nature of feedback loops is so complex that how Notch integrates a modulating function with other signaling pathways to provide developmental accuracy to individual cellular and microenvironmental effects is mysterious. Oncogenic Notch signaling and its relationship with other signaling pathways have been specifically observed in various hematopoietic malignancies, T-cell acute lymphoblastic leukemia, and solid malignancies, including ovarian, lung, hepatocellular, breast, and colon cancers. Recent studies reveal that Notch signaling influences tumor growth and spread in a complex manner that involves intrinsic cell fate alterations, niche remodeling, and modulation of the immune response. This review discusses the reciprocal regulation of the Notch signaling pathway and other signaling transductions in hematopoiesis, thymocyte development, organ development, and tumorigenesis.

Notch Signaling Modulation as Therapeutic Strategy

One of the most studied therapeutic strategies for Notch-related diseases is the use of gamma-secretase inhibitors, which block Notch intracellular domain release from the membrane, cutting one of the cleavage products. This strategy has been used as an antitumor therapy due to the aberrant and continuous activation of Notch that is common in cancer. This treatment has shown good results in some types of diseases; however, given the essential functions of Notch in the maintenance and survival of stem cells in some tissues, its long-term use can lead to many toxic side effects, limiting its use. Furthermore, due to the cross-signaling with different pathways stemming from the aberrant and continuous activation of Notch in cancers, it is necessary to explore more specific drugs that only target Notch receptors, especially Notch 1-3, which seem to be more associated with cancer. Although several Notch signaling inhibitors, known as Notch signaling modulators, have been discovered, none of the developed or discovered Notch pathway modulating agents specifically in clinical trials were actually able to inhibit this stem cell renewal meant for chemotherapy.

Another therapeutic strategy explored was the use of monoclonal antibodies that specifically prevent the interaction of ligands with Notch, decreasing the release of NIC. In preclinical studies, monoclonal antibodies have shown promise in reducing tumor growth by inhibiting Notch signaling. However, it is not yet known if this strategy presents disadvantageous adverse events. The development of promising alternatives for cancer treatment is mainly due to the different and divergent functions of Notch in cancer, exerting the function either of a tumor-stimulating or tumor-suppressing gene and the gene-gene or gene-environment interactions. Thus, it is important to identify a reliable predictive biomarker of activity in cancer progression. Furthermore, the identification of the main subgroups of patients that may benefit from this strategy is crucial. Such information is particularly important in therapy, since amplification was

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presented as a potential therapeutic target and was suggested to be responsible for drug resistance to Notch-targeted therapy.

Future Perspectives

We have already gathered robust evidence implicating the Notch cascade in a great variety of disorders described in this review. Therefore, by targeting the pharmacology section, we have only considered the diseases of greatest public health interest. While it is not realistic to theorize in one chapter on prospective potent drugs acting on Notch signaling, this section will walk you through how the worldwide scientific community is getting closer to reverting and/or arresting Notch to treat the most severe diseases. We first summarize the candidates for all the Notch components involved – from ligand to cofactors. Then, we detail the Notch inhibitors, the competition in their development, and trials involving Notch. Finally, we review Notch therapy bioengineering and concerns about preclinical studies.

Future Perspectives for Notch Signaling Inhibition. The ever-growing pace of deciphering Notch cell signaling has yielded a remarkable set of potential therapeutic targets. That collection of molecules may be further outlined in terms of efficacy, pharmacological parameters, and research settings by its relationship with a) Notch cellular location; b) Notch modulatory, activating/transactivation, inhibitory/cis-inhibition, and signaling disrupting phase of action; c) ligand/receptor/cofactors implicated component. The most prevalent and directly targeted disease category facing a plethora of Notch-related candidates at the proof-of-concept/event-preemptive/juvenile clinical trials stage is secretory-expressive malignancies. These enzymes/kinases and synthetic capping and cysteine-shaving peptidomimetics aim to target and disrupt Notch's extracellular and transcriptional-dependent control of gene expression to block cellular proliferation and/or death resistance for endometrium, embryonal/germline, mesenchymal, and mature epithelial cancers, including embryo strip and/or pregnancy/fertility-related complications such as miscarriage and placental abnormalities.

Conclusion

Much effort has been made in studies on Notch signaling in recent years. The present review briefly summarizes the current findings on Notch signaling in the regulation of various stem cell populations potentially involved in the pathogenesis of some diseases, together with the possible role of Notch signaling in the progression of these diseases. Potential therapeutic targets for these diseases could be identified based on the disruption of Notch signaling. Although the current studies provide useful information for a better understanding of this complex pathway, more detailed work is necessary for a definitive understanding of the precise actions of Notch signaling in the pathogenesis of these diseases. First of all, future work should focus on the correlation between the gain or loss of function of Notch and the cell fate commitment of various cell populations and the progression of some human diseases.

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Additional correlative studies should also analyze whether Notch is a critical element of signal transduction pathways known to be important in these different biological contexts. These studies could potentially provide a stronger rationale for the development of drugs that are targeted against Notch signaling as novel therapeutic strategies to affect the course of these diseases. Additionally, clarification of the cascade related to Notch signaling, and which genes are regulated by downstream effectors of Notch signaling, will definitively identify the molecular mechanisms of Notch signaling in the above processes, possibly revealing unexpected relationships and novel regulators for Notch activity in each context. Ultimately, the elucidation of these underlying causes and effects could lead to a more attractive therapeutic target aimed at interrupting diseases in which Notch pathway dysregulation is involved at their very sources.

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Authors' contributions

All authors shared in the conception and design and interpretation of data, drafting of the manuscript and critical revision of the case study for intellectual content and final approval of the version to be published. All authors read and approved the final manuscript.

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