NOTCH Signaling in Osteosarcoma

Subjects: Oncology

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Osteosarcoma is the most common primary malignant tumor of bones. Most osteosarcoma patients currently receive combinatorial treatment of doxorubicin, cisplatin, and methotrexate as the first-line therapy; however, local recurrence and lung metastasis rates remain high. Despite the numerous trials conducted to evaluate novel therapies for metastatic osteosarcoma, the long-term survival of patients remains dismally bad. Studies have reported abnormal activation of the NOTCH signaling pathway in most clinical specimens of osteosarcoma, which is closely related to a poor prognosis. Similarly, studies have reported that NOTCH signaling affected the biological behavior of osteosarcoma through various molecular mechanisms. NOTCH-targeted therapy has shown potential for the treatment of osteosarcoma in clinical research.

osteosarcoma NOTCH signaling prognosis molecular targeted therapy

1. Introduction

Osteosarcoma is the most common primary malignant tumor of bones[1]. Most osteosarcoma patients currently receive combinatorial treatment of doxorubicin, cisplatin, and methotrexate as the first-line therapy; however, local recurrence and lung metastasis rates remain high[2][3][4]. Despite the numerous trials conducted to evaluate novel therapies for metastatic osteosarcoma, the long-term survival of patients remains dismally bad[5][6][7]. Tyrosine kinase inhibitors such as regorafenib have been the major drug for treating metastatic osteosarcoma[8]. Other drug classes have been trialed for metastatic osteosarcoma based on promising pre-clinical data but have yielded generally disappointing outcomes[9][10].

A potential relationship exists between the occurrence and progression of osteosarcoma and bone differentiation defects[11][12]. NOTCH signaling is an important mechanism regulating the normal development and differentiation of bone[13]. Clinical studies have reported abnormal activation of the NOTCH signaling pathway in most specimens of osteosarcoma, which is closely related to a poor prognosis. Similarly, NOTCH signaling has been proved to affect the biological behavior of osteosarcoma through various molecular mechanisms. Recent clinical trials have reported suitable efficacy for the treatment of osteosarcoma with the strategy of inhibition of the expression and function of the NOTCH pathway. Therefore, evaluating the potential of therapeutics targeting NOTCH for the treatment of osteosarcoma is of practical clinical importance. However, the positive or negative effect of the pathway on cancers has not been identified clearly. Recent clinical trials have reported suitable efficacy for the treatment of osteosarcoma with the strategy of inhibition of the expression and function of the NOTCH pathway. To date, systematic reviews[14][15][16] published have not been concerned with the topic of the clinical significance of

the alteration of the expression and the dysfunction of the NOTCH pathway in osteosarcoma. Furthermore, the latest research advances in the NOTCH pathway in osteosarcoma were summarized in this research.

2. Composition of NOTCH Signaling

The NOTCH signaling pathway is composed of NOTCH ligand, NOTCH receptor, related enzymes, transcription factor CSL, regulatory factor, and NOTCH signaling downstream molecules[17] (**Figure 1**). NOTCH ligands, namely Delta/Serrate/Lag2 (DSL) family, belong to one-way transmembrane proteins. Mammals have five DSL ligands: Dll1, Dll4, and Dll3 are members of the delta-like ligand family; Jag1 and Jag2 are members of the serrate ligand family[18]. The NOTCH receptors, a series of transmembrane glycoproteins, are composed of extracellular regions, transmembrane regions, and cytoplasmic regions[19].The NOTCH receptors (NOTCH1-4), encoded by different genes, differ in structures and can be degraded by a variety of proteases[20]. The cleaved NOTCH intracellular domain (NICD) is released into the cytoplasm and then transported to the nucleus to form the NOTCH transcription complex (NTC), which is composed of NICD, DNA binding factor, and transcriptional coactivators[20]. After combining with NOTCH regulatory element (NRE), NTC recruits transcription coregulatory factors and starts the transcription of the specific target genes (such as Hes1, Hes5, etc.)[20]. The signaling cascade of the NOTCH pathway often begins with the interaction between the NOTCH receptor and the DSL ligand[21]. DSL ligands activate specific NOTCH receptors and induce their cleavage. Then NOTCH intracellular domain (NICD) is released and transported to the nucleus, thus forming NOTCH transcription complex (NTC) with transcription factor CSL, which acts as a transcription coactivator to start the transcription of NOTCH target genes[21].

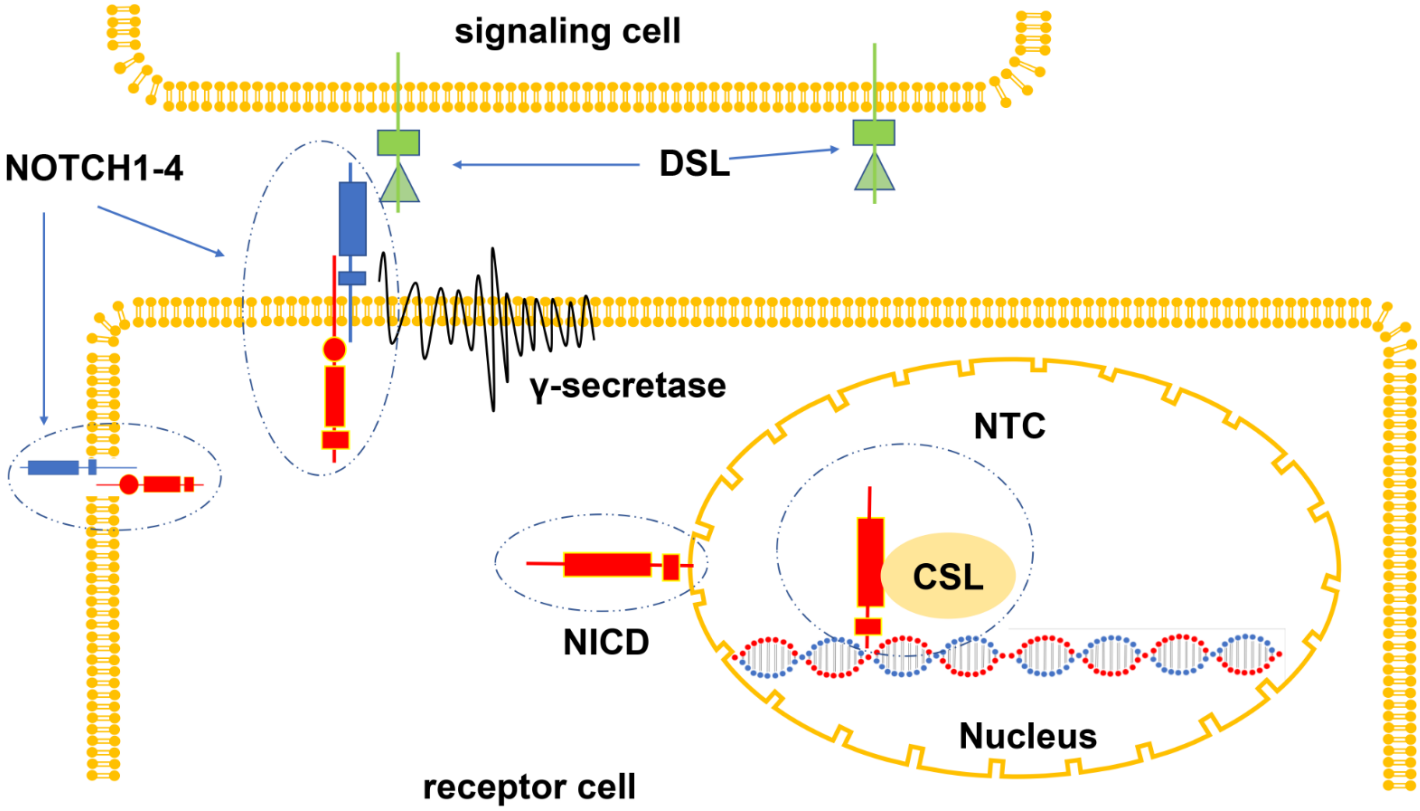

Figure 1. The Notch signaling pathway.

3. Biological Functions of NOTCH Signaling

The NOTCH pathway modulates cell fate through adjusting signal intensities and dynamics as well as the diversity of ligand-receptor binding[22][23][24]. Under physiological conditions, NOTCH signaling regulates and determines the fate of different tissues and cells during embryonic development[25]. The NOTCH signaling pathway also has a profound effect on tumors, however, the positive or negative effect has not been identified clearly.

4. Clinical Significance of NOTCH Signaling Dysfunction in Osteosarcoma

The clinical significance of the dysfunction of the NOTCH signaling pathway in osteosarcoma was confirmed by the results of many published studies involving several proteins of the pathway signaling. Those results showed that the NOTCH signaling pathway played an important role in promoting osteosarcoma, and its abnormal activation rather than inactivation accelerates the malignant progression. Therefore, evaluating its expression level and functional status might be significant in predicting the development and prognosis of osteosarcoma. In conclusion, the results showed that the NOTCH signaling pathway played an important role in promoting osteosarcoma, and its abnormal activation rather than inactivation accelerates the malignant progression. Therefore, evaluating its expression level and functional status might be significant in predicting the development and prognosis of osteosarcoma.

5. Effects of NOTCH Signaling Pathway on Osteosarcoma

Studies found that the effects of the NOTCH pathway varied among different osteosarcoma cell lines, including effects on proliferation, migration and invasion, drug resistance, and cancer stem cell characteristics. In addition, NOTCH signaling also has an important impact on the microenvironment of osteosarcoma via modulating immune function, tumor angiogenesis, and osteogenic differentiation, which indirectly affect the biological behavior of osteosarcoma (**Figure 2**).

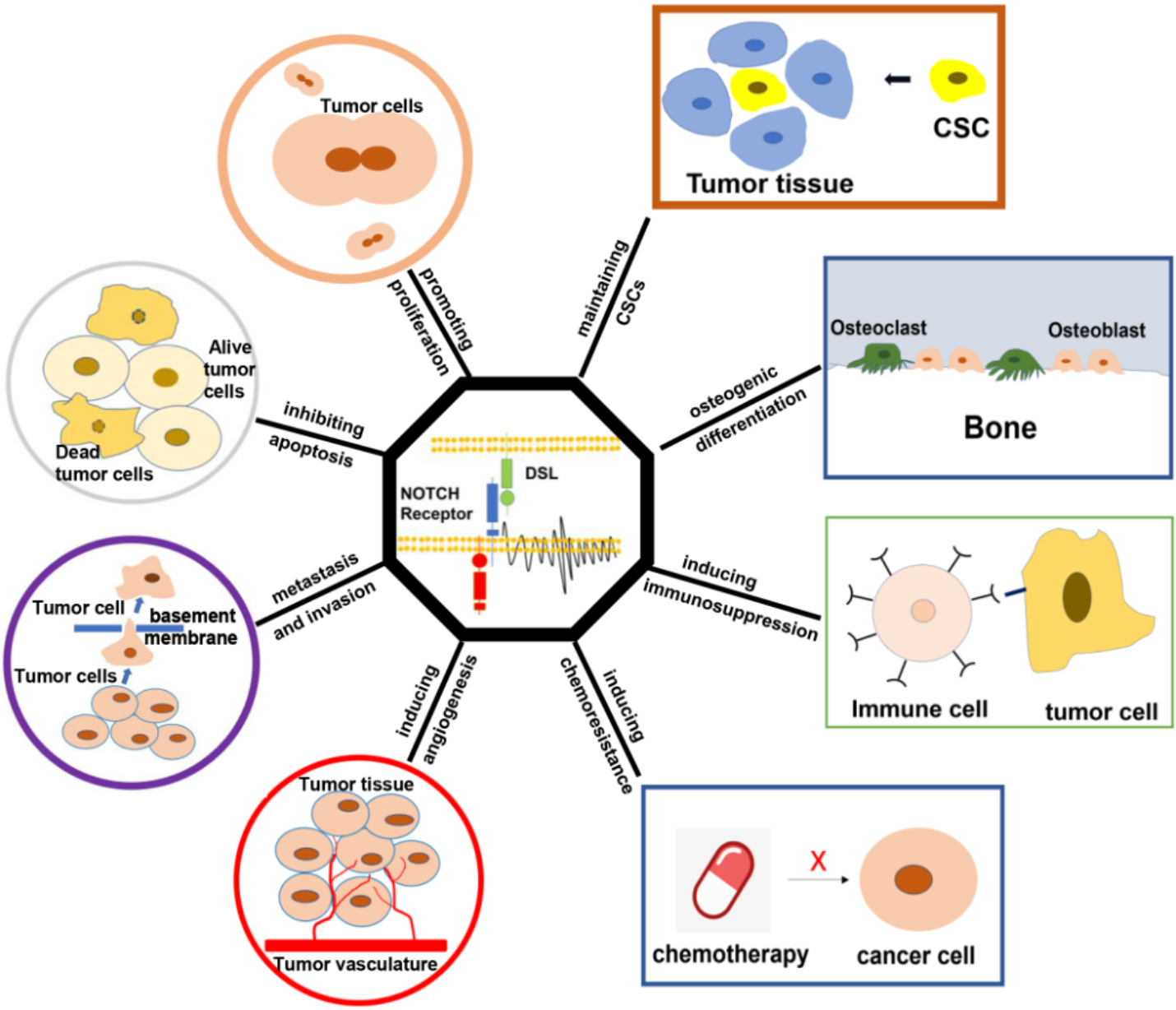

Figure 2. Effect of the NOTCH signaling pathway on osteosarcoma.

6. NOTCH Signaling in Animal Models of Osteosarcoma

An ideal animal model of cancer is of extreme significance for the understanding of the mechanism of tumor occurrence as well as for the development of new drugs[26]. To date, the commonly used animal model of osteosarcoma is the tumor transplantation model, which can be divided into the xenograft model (human osteosarcoma animal transplantation) and the allograft model based on the different cell line sources of the host and cells (or tissues)[27]. Currently, the model of concern is the emerging genetically engineered animal tumor model[28]. The following sections review the research progress on the NOTCH signaling pathway in animal models of osteosarcoma.

7. Osteosarcoma Treatment Strategy Based on NOTCH Signaling

The NOTCH pathway, a potential target for tumor therapy, is actively involved in tumor growth, metastasis, chemoresistance, tumor immunity, and other functions. The current therapeutic strategies mostly inhibit the NOTCH pathway to exert antitumor effects[29]. There are mainly two types of NOTCH inhibitors: selective and non-selective. Selective inhibitors include the application of antisense RNA, interfering RNA, and monoclonal antibodies, while non-selective inhibitors include ligand-blocking agents, γ- Secretion inhibitors, and some natural compounds. Selective inhibitors have strong specificity, minimal side effects, and do not easily induce drug resistance. Non-selective inhibitors are more toxic; however, considering the diversity of the NOTCH pathway in cancers, these inhibitors have more clinical value in some cases. Furthermore, numerous natural products and their extracts have been found to inhibit the NOTCH pathway to exert anticancer effects.

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