Extended Abstract International Journal of Inflammation, Cancer and Integrative Therapy
2020
Vol.7 No.1

The role of Wnt signaling and treatment mechanism in leukemia

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Abstract Objective:

Increased activity of Wnt pathway has been observed in a huge number of malignancies. This pathway can function as a prosurvival factor in leukemia stem cells and early committed leukemic precursors and its inhibition is regarded as a therapeutic approach. Accordingly, the aim of this review is to evaluate the Wnt inhibitors used in leukemia models. Discussion: Inhibition of the Wnt pathway has been reported to have beneficial therapeutic effects in leukemia, both in vitro in leukemia cell lines and in vivo in animal models. Overall, the use Wnt inhibitor in CML, AML, APL, CLL, B-ALL and T-ALL has a better therapeutic effect than conventional treatments. Conclusions: Clearly, precise modulation of the Wnt pathway will be necessary to balance anti-tumor efficacy with adverse eventsand will be a challenge for ongoing and future leukemia patients. Despite these concerns, new regulators of the Wnt signaling cascade offer the opportunity for us to increase our comprehension of this exceedingly complex pathway and potentially for the treatment.

Introduction

Acute myeloid leukemia (AML) is a clonal disease resulting from a malignant transformation of a hematopoietic stem or progenitor cell. It is characterized by an abnormal accumulation of hematopoietic progenitor cells leading to progressive insufficiency of normal hematopoiesis. Over the last decades, considerable progress has been achieved in the elucidation of the molecular pathogenesis of this disease. The major types of genetic events in the development of AML comprise alterations in myeloid transcription factors and activating mutations of signal transduction intermediates leading to inappropriate gene expression and aberrant signal transduction, respectively. Both mechanisms are highly interdependent, resulting in reduced apoptosis, increased stem cell self-renewal and blocked differentiation of AML cells.1 It is supposed that AML arises from the malignant transformation of a normal hematopoietic stem or progenitor cell into a cancer stem cell. Normal embryonic and hematopoietic stem cells (HSCs) possess the unique properties of self-renewal and the ability to develop into multiple lineages with generation of more differentiated progenies.2 Therefore, HSCs are considered to be *bona fide* candidates for the accumulation of multistep, genetic mutations transforming them into a cancer stem cell. Another hypothesis is that hematopoietic progenitor cells may regain stem cell properties owing to oncogenic mutations finally leading to the initiation of leukemia. In various types of leukemia, cancer stem cells have been detected, and several features of these leukemia stem cells (LSCs) have been described. The LSC concept is well established in myeloid leukemia.

The canonical Wnt pathway

The Wnt pathway is evolutionary highly conserved and plays a critical role in the development of many organ systems. The human genome harbors almost 20 Wnt genes, all of which encode lipid-modified secreted glycoproteins regulating developmental processes. Three different intracellular Wnt signaling pathways have been described including the canonical pathway, an only partially understood pathway involving calcium ions, and the planar-cell-polarity pathway.

Other mechanisms of aberrant Wnt signaling in AML

A considerable fraction of AML patients does show neither Flt3 mutations nor balanced translocations. Recent studies revealed aberrant Wnt signaling in AML cells that is independent from the occurrence of AML-associated fusion proteins or Flt3-ITD mutations.

Conclusion

AML is often characterized by activation of Wnt signaling and downstream effectors. An important step forward will be to analyze the therapeutic potential of this pathway in acute leukemias. Activated Wnt signaling is frequently found in various human cancers. Therefore, inhibition of this pathway might be a promising therapeutic target for cancer therapy. Imatinib effectively inhibits constitutive activity of *β*-catenin signaling and suppresses proliferation of human colon cancer cells. In a conditional Wnt-1 transgenic mouse tumor model, reduction of Wnt-1 signaling resulted in the regression of the Wnt-1 initiated primary mammary tumors and lung metastasis. Moreover, blockade of Wnt signaling by either siRNA or use of specific antibodies inhibits tumor growth and induces apoptosis of cancer cells. Mazieres *et al*., could show that inhibition of Wnt16 by the use of siRNA and an anti-Wnt16 antibody induces apoptosis in human ALL cells containing the t(1;19) translocation. Targeted Wnt blockage has to be handled with care to minimize risk for derogations of normal hematopoiesis. However, inhibition of Wnt signaling may provide a basis for the more selective targeting of cancer stem cells in leukemia.

References

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This work is partly presented at Joint Event on 2nd Global Summit on Oncology & Cancer March 12-14, 2018 Singapore