13 Mechanisms of TGF-β-Induced Apoptosis in Cancer Cells

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CONTENTS

SUMMARY
INTRODUCTION
MOLECULAR MECHANISMS OF TGF-β-INDUCED APOPTOSIS
CONCLUSION
ACKNOWLEDGMENTS
REFERENCES

Abstract

Apoptosis is a common regulatory process of multicellular organisms. Transforming growth factor beta (TGF-β) has essential roles in a variety of apoptotic pathways including the mitochondrial apoptotic, death receptor, and other intracellular signaling pathways. The TGF-β-mediated apoptotic process involves not only intracellular proapoptotic responses but also anti-apoptotic signals. Resistance to TGF-β regulatory signals is the most indicative characteristic of many cancer cells during tumorigenesis. Therefore, controlling the homeostatic balance of these regulatory signals is critical for the prevention of tumorigenesis. Understanding the mechanisms of TGF-β-induced apoptosis in cancer cells will provide new insight of anticancer therapy.

Key Words: TGF-β; apoptosis; hepatoma; gastric cancer.

1. INTRODUCTION

Apoptosis, a particular morphological manifestation of programmed cell death, is a common regulatory process of multicellular organisms. The term apoptosis has been used as an active process that depends on the execution of a defined sequence of signaling events that lead to cell demise. It is a precisely regulated phenomenon essential for many biological processes, such as embryonic development, regulation of the immune system, and normal homeostasis of multicellular organisms (1–3). Apoptosis also operates in adult organisms to maintain normal cellular homeostasis, which is particularly important with respect to the development of disease in human beings. During the past two decades, hundreds of genes that control the initiation, execution, and regulation of apoptosis have been explored. Among them, TGF-β plays an important role in apoptosis in vivo and in vitro. TGF-β-mediated apoptosis is involved in the elimination of damaged or abnormal cells from normal tissue in vivo, and these apoptotic effects are shown in various cell types as described in Table 1. The TGF-β-mediated apoptotic process involves not only intracellular proapoptotic...
responses but also antiapoptotic signals. TGF-β provides signals for both cell survival and apoptosis depending upon the cell type and physiological context. Cancer cells become refractory to this regulatory signal and thus do not undergo apoptosis under appropriate conditions. In most cases, the TGF-β signaling pathway is proapoptotic, but the molecular mechanism that allows TGF-β to induce apoptosis is still controversial. However, the homeostatic balance of these regulatory signals is critical for the prevention of tumorigenesis. In this review, we summarize the molecular mechanism of TGF-β-induced apoptosis in a variety of human cancers. Understanding the mechanisms of TGF-β-induced apoptosis in normal and cancer cells will provide new insight of anticancer therapy because increasing the sensitivity of tumor cells to anticancer therapy is tightly correlated with the induction of apoptosis by anticancer drugs.

2. MOLECULAR MECHANISMS OF TGF-β-INDUCED APOPTOSIS

2.1. Hepatoma

The growth and mass of the liver can be regulated during development and adult life. Liver cells proliferate during the postnatal period, whereas adult hepatocytes no longer actively proliferate. After injury to the liver by partial hepatectomy, the liver can regenerate. This regeneration process involves a wide variety of growth factors controlling proliferation, apoptosis, and differentiation. Many observations indicate that TGF-β plays an important role in hepatocyte growth inhibition and is a potent inducer of apoptosis in the liver (4,5). The molecular mechanism of TGF-β-induced apoptosis has been studied in the hepatoma