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Review Article

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XIAP-AS1 is a New Long Non Coding RNA

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Abstract

Dysregulation of long non-coding RNAs (lncRNAs) is reported to be associated with the development and progression of various cancers. XIAP-AS1 is a novel lncRNA. It has been shown that XIAP-AS1 is transcribed from the first intron of the complementary strand of the XIAP gene. XIAP-AS1 is located primarily in the nucleus. LncRNA XIAP-AS1 can regulate apoptosis in gastric cancer and might serve as a potential oncogene for colon cancer. Sp1 is a responsible transcription factor for transcription of the XIAP gene. XIAP-AS1 RNA interacts with Sp1 and thereby participates in XIAP transcription. XIAP-AS1 knockingdown decreases the binding of Sp1 to the promoter region of XIAP. In gastric tumor cells, XIAP-AS1 knockdown promotes tumor necrosis factor (TNF)-related apoptosis-inducing ligand (TRAIL)-induced apoptosis. XIAP-AS1 knockdown blockes cell invasion of colon cancer cells by regulating the expression of EMT markers, such as E-cadherin, ZO-1, vimentin, and N-cadherin. Moreover, XIAP-AS1 knockdown significantly reduces STAT3 phosphorylation. XIAP-AS1 interacts with Sp1 and is involved in XIAP transcription. In gastric cancer cells, XIAP-AS1 is a potential target for TRAIL-induced apoptosis. XIAP-AS1 is significantly increased in CRC tissues and moreover its expression showes a positive correlation with TNM stage and cumulative survival rate of CRC. In this review, we focus on the importance of new lncRNA XIAP-AS1 in tumorigenesis, as it functions in apoptosis.

Keywords

Apoptosis; Cancer; Sp1; lncRNA XIAP-AS1; XIAP

Introduction

Cancer is a very complex disease associated with a wide range of genetic mutations, epigenetic alterations, chromosomal translocations, amplification and deletions [1]. LncRNA is a group of non-coding RNAs that is more than 200 base pairs [2], generally do not code for proteins, and is associated with diverse functions [3], such as patient outcome, cell proliferation, cell apoptosis, cell metastasis and invasion, cell cycle, epithelial-mesenchymal transition (EMT), cancer stem cells (CSCs) and drug resistance [4].

LncRNAs has been one of the important research fields in the cancer biology, as they function in tumorigenesis, for example MALAT1 is involved in a variety of human cancers including breast, prostate, liver, colon, uterus, pancreatic, ovarian,and hematological malignancies and neuroblastoma [5,6]. High HOTAIR expression is correlated tightly with the presence of liver metastasis, and is demonstrated in gastric cancer [7]. ZEB1-AS1 overexpression can facilitate cell growth by promoting p21-activated kinases 2 (PAK2) expression by sponging miR-455-3p in colon adenocarcinoma cells [4].

Apoptosis is a very tightly programmed cell death with a number of enzyme-dependent biochemical processes [8,9]. Apoptosis can be triggered by signals from within the cell (intrinsic or mitochondrial pathway), or by extrinsic signals (extrinsic or death receptor pathway). Defect in apoptosis can cause cancer or autoimmunity [8, 10,11]. Caspases (cysteine-aspartic proteases) are proteolytic enzymes largely known for their role in controlling inflammation and cell death [12]. Mammalian caspase -2, -3, -7, -8, -9 and -10 are shown to be apoptotic caspases [12]. They are subdivided into the initiators and the effectors based on the presence or absence of specific-protein interaction domains toward the N-terminus. Initiator caspases include death effector domains (DED; caspase -8 and -10) or caspase-recruitment domains (CARD; caspase -2, -9, -1 and -11), which mediate their dimerization and/or recruitment into larger complexes to facilitate their activation [12]. Negative regulation of caspases function is achieved by IAP proteins family, they regulate both the intrinsic and extrinsic pathways. Principally eight members of IAP proteins in humans have been identified; these are NAIP (BIRC1), cIAP1 (BIRC2), cIAP2 (BIRC3), X-linked IAP (XIAP, BIRC4), Survivin (BIRC5), Apollon (BRUCE, BIRC6), Livin/ML-IAP (BIRC7), and IAP-like protein 2 (ILP2 – BIRC8). XIAP (X-linked mammalian inhibitor of apoptosis protein) and survivin remain the better-known members, and characterized IAP members so far. XIAP anti-apoptotic activity includes inhibition of active executor capsases as well as prevention of initiator caspase-9 activation [10,11,13]. IAPs are overexpressed in many cancers. Targeting IAP-family members XIAP, cIAP1, Survivin, or Apollon induce apoptosis [8]. Caspases -3 and -7, as well as caspase-9 (intrinsic pathway), are directly affected by the human IAP family members, XIAP, cIAP1, and cIAP2 [8]. XIAP is the most potent inhibitor of caspases and apoptosis among IAPs, and is involved in cascades of many transcription factors [14, 15]. Expression of XIAP is elevated in many cancers, including colon, ovarian, lung, kidney cancers, and myeloid leukemia [16].

Cellular IAPs (cIAP1 and cIAP2) have similar roles as XIAP in regulating caspases activity, but are also involved in regulating NF-κB pathways [17]. Two typical prosurvival NF-κB targets are Bcl-xL and XIAP, which can block apoptosis at multiple steps [8]. Disrupted mitochondria also produce second mitochondria derived activator of caspase (SMAC; also known as DIABLO), which releases caspase 3 from Xlinked inhibitor of apoptosis (XIAP)mediated inhibition [18]. XIAP is a direct inhibitor of caspase-3 and caspase-9 and modulates the Bax/cytochrome c pathway by inhibiting caspase-9 [15]. XIAP binds in vitro to effector caspases-3 and -7 as well as to caspase-9, a protease that plays an important role in the processing of both caspases-3 and -7 [19]. XIAP down-regulation is an important for caspase activation in response to various apoptotic stimuli [15]. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a member of the tumor necrosis factor family of ligands [19]. TRAIL initiates apoptosis by a pathway triggered by its interaction with death receptors [19]. TRAIL is shown to represent a targeted therapy against cancer because it induces apoptosis only in tumor cells [20]. Many

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leukemic cells shows XIAP overexpression [20]. The interaction between TRAIL and proteasome inhibitors is a promising approach to induce cell death in tumor cells [21]. The sensitivity of cancer cells to TRAIL can be increased by inhibiting the function of XIAP [19]. In colon cancer, XIAP up-regulation inhibits not only apoptosis but also autophagy [14].

XIAP-AS1 is a novel lncRNA, interacts with Sp1 to regulate XIAP transcription

Sp1 is an important basal transcription factor that is required for transcription of a large number of "housekeeping genes" [22]. Specificity protein (Sp) transcription factors (TFs) Sp1, Sp3, and Sp4 are members of the Sp/Krüppel-like family (KLF) and Sp1 has been the most extensively investigated member of this family. Sp proteins play an important role in embryonic growth and early postnatal development, differentiation, cell cycle regulation, and multiple diseases [23,24]. Sp1 is a constitutive transcription factor [25], its protein levels can vary significantly in different tissues [25].

X-linked inhibitor of apoptosis (XIAP) is the most potent member of the inhibitors of apoptosis proteins (IAP) gene family. XIAP binds to and inhibits caspase (CASP) 3, 7, and 9 and therefore suppresses various agent-induced cell apoptosis [16]. Sp1 is a very smart transcription factor, which binds to the GC-box site of the XIAP promoter[15]. XIAP-AS1 is a novel lncRNA, derived from the complementary strand of the XIAP gene. lncRNA, XIAP-AS1 plays a role in the transcription of XIAP by interacting with Sp1 [26].

XIAP-AS1 functions in colorectal and gastric cancers

Colorectal cancer is the second most common malignancy and cause of cancer-related mortality. The most common site of colorectal cancer metastases is the liver, and it is often the only site involved [27]. Different types noncoding RNAs (ncRNAs), such as long noncoding RNAs (lncRNAs), microRNAs (miRNAs), and circular RNAs (circRNAs), are critically involved in gastric cancer development. Several lncRNAs, miRNAs, and circRNAs play an essential role in gastric cancer drug resistance, especially in chemoresistance [28].

LncRNA XIAP-AS1 expression of is significantly increased in CRC tissues [29]. XIAP-AS1 expression is increased in CRC tissues and a high expression level of XIAP-AS1 in colon cancer patients is positively correlated with TNM stage [29]. Silencing of XIAP-AS1 decreases the expression of E-cadherin (E-cad) and ZO-1 but increases the expression of vimentin and N-cadherin, suggesting that XIAP-AS1 might have an important potential role in facilitating EMT colon carcinoma. Knockingdown of XIAP-AS1 significantly suppresses CRC cell growth and arrested the cell cycle at the G0/G1 phase. Cell-cycle-related genes cyclin D, cyclin A, and cyclin E are regulated by XIAP-AS1 silencing [29]. XIAP-AS1 knockdown significantly reduces the expression level of b-catenin in colon cancer, implying that XIAP-AS1 promoted cell growth and invasion by potentiating the Wnt/b-catenin pathway. Increased expressions of cyclin D1, cyclin E, and c-Myc have been reported in colon cancer. XIAP-AS1 silencing causes G0/G1 phase cell-cycle arrest via downregulation of cyclin D1, cyclin E, and c-Myc levels, which appears to be the underlying mechanism in colon cancer cell growth inhibition [29]. XIAP-AS1 is involved in XIAP transcription by interacting with Sp1. XIAP-AS1 enhance the binding of Sp1 to the XIAP gene promoter. XIAP-AS1 knockdown promotes TRAIL-induced apoptosis in gastric tumor cells, suggesting XIAP-AS1 as a potential therapeutic target for regulating TRAIL induced cell death in gastric tumor cells [26]. Initiation and execution of such processes are regulated by the BCL-2 and caspase families of proteins [30]. Activation of Bax and Bak, BCL-2 family members, results in MOMP and the release of pro-apoptotic proteins, including cytochrome c, from the inter-membrane space into the cytosol. Cytochrome c can then bind Apaf-1 forming the apoptosome and activating caspase-9. Once activated, caspase-9 directly cleaves and activates caspase-3 and caspase-7 [30]. XIAP prevents cell apoptosis by blocking the activation and maturation of caspase-3/-7/-9 [14].

XIAP-AS1 interacts with Sp1 to regulate XIAP transcription. Down-regulation of XIAP-AS1 results in XIAP knockdown and subsequent caspase-9 activation. In turn, Caspase-3 activates caspase-9 through a feedback amplification loop in which caspase-3 cleaves the N-terminal region of caspase-9 and inactivates XIAP itself [26]. LncRNA XIAP-AS1 can promote cell growth and invasion by facilitating the Wnt/b-catenin pathway and EMT. XIAP-AS1 plays an oncogenic role in colon cancer progression and serves as a potential target for cancer prevention and treatment [29]. XIAP-AS1 plays an oncogenic role by interfering with STAT3 phosphorylation and EMT markers expression [14].

Conclusion and Perspectives

LncRNAs are important regulators of cancer, as they are involved in cell apoptosis, cell proliferation, cell metastasis and invasion, cell cycle, epithelial-mesenchymal transition (EMT). Human IAP family members, XIAP, cIAP1, and cIAP2 directly affect Caspases-3 and -7, as well as caspase -9. XIAP-AS1 is a newly identified LncRNA that regulated XIAP transcription through interacting with Sp1, and functionsin tumorigenesis. Expression of LncRNA XIAP-AS1 is significantly increased in CRC tissues, and moreover it can regulate apoptosis in gastric cancer cells. Its knockdown promotes TRAIL-induced apoptosis in gastric tumor cells. Therefore conclude that as XIAP-AS enhances XIAP transcription via interacting with Sp1 and that XIAP-AS may be a potential therapeutic target for gastric cancer. And to speculate that XIAP-AS1 plays an oncogenic role in colon cancer progression and serves as a potential target for cancer prevention and treatment. The function of XIAP-AS1 is currently still unclear.

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