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Ago2 is a Novel Target for Hepatocellular Carcinoma

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Abstract

Argonaute 2 (Ago2, EIF2C2) is one of the very important members of RNA-induced silencing complex (RISC). It's a ribonuclease enzyme and has a strong catalytic activity and plays major role in post-transcriptional gene regulation during small RNAs guided gene silencing processes through RISC activity. Ago2 is a multifaceted protein and in detail structural elucidations have provided new insights into minute details and functional mechanisms of the four major domains of this protein. Recent studies have clearly shown that Ago2 has miRNAs dependent as well as independent role in gene regulation and it is overexpressed in many cancers and involved in development and progression of various types of cancers including Hepatocellular Carcinoma (HCC). Due to its abundance in HCC, it is involved in regulation of oncogenes and tumor suppressor genes and various hallmarks of Hepatocarcinogenesis. This mini review briefly discusses the role of Ago2 in the development and progression of HCC and its therapeutic aspects.

Keywords: Argonaute 2; Risc; HCC; Gene regulation; Mirna

Introduction

RNA-induced silencing complex or RISC assembly plays major role in eukaryotic gene regulation [1]. This RISC is multiprotein complex present in GW/Processing bodies (p-bodies) of eukaryotic cells and Ago2 also termed as EIF2C2 and it is one of the major components of the RISC assembly [2,3]. It belongs to the highly conserved Argonaute family and has structurally very important PIWI domain and crescent PAZ domain along with N domain and MID domain [4]. Human Ago2 has a ribonuclease activity and is the only member of Ago family proteins with the ability of catalytic function [1,4]. It acts as a major partner and has a functional role within the RISC complex during RNA interference activity and post transcriptionally regulates various gene expression [2,3,5]. This enzymatic role of Ago2 along with SND1, another known ribonuclease component of RISC complex and together these two proteins degrade thousands of miRNA-mRNA complexes in eukaryotic cells [6].

Molecular structure of Ago2

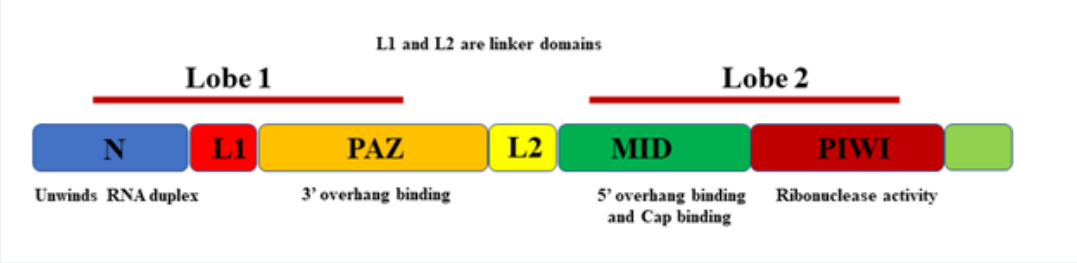

Figure 1: The Structure of Some Anticancer Natural Products Drugs.

Basic understanding of the individual amino acids and molecular structure of the protein and its corresponding gene structure will aid in drug designing. Human Ago2 gene is located on the chromosome number 8 [7]. It is known that Ago2 is ribonuclease enzyme and degrades various RNAs more specifically miRNA-mRNA complex [1-3]. Various elegant studies have shown that Ago2 has four core domains and these four domains array into a two lobes or bi-lobe format consisting of N and PAZ and MID and PIWI domains and the N and PAZ domains are connected by Linker 1 and PAZ and MID domains are connected by Linker 2. MID and PIWI domains are attached to each other as shown in Figure 1 [4,5]. All the four domains are very essential and required for RISC function and activity. The N domain aids in unwinding RNA duplex, The PAZ domain

is involved with 3' overhang binding (RNA binding), The MID domain is associated with 5' overhang binding and CAP binding and finally PIWI domain plays an enzymatic or catalytic role and degrades various miRNA-mRNA duplexes. In detail study of this structure will definitely help in targeting Ago2 enzyme as well as complete RISC assembly for the treatment of various chronic maladies.

Ago2 in HCC

Acetylation of Ago2 protein promotes lung cancer progression [8]. Ago2 expression is also associated with breast cancer [9]. It is also known that increased RISC activity contributes to HCC growth, development and progression [10]. Overexpression of Ago2 promotes angiogenesis via the PTEN/VEGF signaling pathway and tumor metastasis via focal adhesion kinase expression in HCC [11,12] (Figure 2). The miR-99a directly regulates Ago2 expression in HCC through translational repression [13]. Ago2 interacts with PABPC1 and regulates the microRNA mediated gene silencing via RISC assembly in high grade HCC [14]. This complex and its components along with miRNAs plays a macro role in development and progression of HCC [10,15-17].

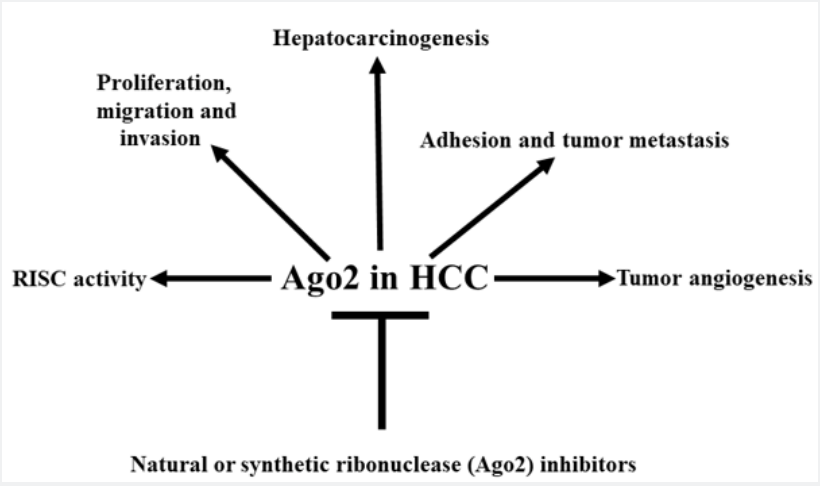

Figure 2: Argonaute 2 is a possible novel therapeutic target for Hepatocellular carcinoma.

Conclusion

RISC complex is a basic and very essential cellular machinery which aids in post transcriptional gene regulation. Being an important component of miRNA associated RISCs machinery, Ago2 has been associated with initiation, development, progression and metastasis of various tumorigenesis in a miRNAs-dependent manner. Ago2 is involved in proliferation, metastasis, angiogenesis, adhesion and metastasis and recent studies have strongly established the direct oncogenic role of Ago2 along with its role in RISC activity. All these evidences strongly suggest that Ago2 is pleotropic protein and has a very important roles in gene regulation and cellular activity. The abundance of this protein in normal cells is very less compared to cancer cells. This protein is highly expressed in hepatocellular carcinoma tissue samples in compared to adjacent normal tissue. In overall summary, the structural, functional and experimental evidences of Ago2 protein have revealed that it has all the features of suitable drug targets of various diseases, based on this it is tempting to speculate that Ago2 is a novel target for Hepatocellular Carcinoma therapy.

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