Role of C14orf166 in viral infection and RNA metabolism and its relationship with cancer (Review)

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Abstract. Chromosome 14 open reading frame 166 (C14orf166) encodes a 28-kDa nuclear and cytoplasmic protein that is involved in viral infection, RNA metabolism, and centrosome structure. It binds to the polymerase acidic protein subunit of the influenza A virus, which is associated with several transcription factors, RNA polymerase II, to activate transcription initiation and promote virus infection. It also interacts with a mature hepatitis C virus core protein to regulate the infection process. In physiological conditions, C14orf166 associates with the proteins, DDX1, HSPC117 and FAM98B, and regulates RNA metabolism and fate. In addition, C14orf166 is overexpressed in a variety of cancer types. Upregulation of C14orf166 may contribute toward cancer malignancy through its impact on glycogen synthase kinase 3β-mediated signaling, the down-regulation of retinoblastoma protein, or the upregulation of IL-6. Therefore, C14orf166 could be used as a biomarker for the diagnosis and prognosis of various cancer types. This review summarized the existent literature about C14orf166, focusing on its functions in physiological and pathological situations.

Contents

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Abbreviations: IAVs, influenza A viruses; NEP, nuclear export protein; PA, polymerase acidic

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1. Introduction

Chromosome 14 open reading frame 166 (C14orf166) is a highly conserved gene that is located on chromosome 14, at the cytogenetic band 14q22.1. It encodes a 28-kDa protein known as C14orf166, CLE, hCLE or CGI-199 that localizes to the nucleus and the cytoplasm. In the developing brain, C14orf166 is a core element of cytosolic RNA granules containing ribosomes that transport specific mRNAs from the cell body to the dendrites, including mRNAs encoding RNA-binding proteins and microtubule-associated proteins, serving a crucial role in local mRNA translation at sites away from the nucleus in neuronal processes (1,2). As the expression of C14orf166 is higher in fetal brain and lungs than in these organs once they are fully developed, it is possible that C14orf166 serves a role in brain and lung organogenesis (3). Furthermore, proteomic analysis of mice brains has demonstrated that C14orf166 is downregulated after embryonic day 15, suggesting its role in cell growth during development (4). In addition, proteomic analysis has demonstrated that C14orf166 is associated with transcriptional-related functions as it is part of the human spliceosome (5) and the tRNA-splicing ligase complex (6), and it interacts with the 7SK snRNA methylphosphate capping enzyme (7). Furthermore, certain studies have reported that C14orf166 may serve an immunogenic role and act as a autoantigen, although this remains to be confirmed (8,9). The present review focuses on the main effects of C14orf166, including its role during viral infections and RNA metabolism, and investigates its potential pathogenic roles of C14orf166 in cancer and the suggested underlying mechanism (Fig. 1).

2. Interaction with influenza A virus (IAV)

IAVs cause an annually recurrent epidemic of acute respiratory disease that poses a major public health problem worldwide. The World Health Organization estimates that the influenza epidemic leads to 3-5 million cases of severe illness and up to 650,000 deaths each year (10). The genome of IAVs consists of eight single-stranded negative-sense viral RNA (vRNA) segments that range between 2,341 and 890 nucleotides in length, and are named after the main protein they encode (11). Regardless of the length of the segment, the 3' and 5'termini of each vRNA are bound to the RNA-dependent

RNA polymerase (RdRp), and the remaining RNA is encapsulated by a nucleoprotein (NP). Therefore, the viral genetic material is packed in a vRNA-NP-RdRp complex (12), also termed viral ribonucleoprotein (vRNP) complex (13). The RdRp from influenza virus is a heterotrimer composed of the polymerase basic proteins 1 (PB1) and 2 (PB2), and polymerase acidic (PA) protein. PB1 is the core subunit of RdRp and harbors the polymerase activity (10). PB2 contains a cap-binding domain that recognizes the capped cellular mRNAs. Following binding to PB2, the cellular mRNAs are cleaved by the endonuclease activity of the PA subunit at ~12 nucleotides away from the 5'-cap. This process, referred to as 'cap-snatching', produces the primers necessary for the viral transcription (14). Therefore, it is an essential step for the transcription of viral RNA in the nucleus of a host cell during influenza virus infection (15,16).

The vRNP complex is hypothesized to be a powerful factor during the invasion of IAV into the host cell. A considerable amount of literature has demonstrated that the nuclear export process depends not only on the formation of a protein complex comprising vRNPs, the viral nuclear export protein (NEP) and the viral matrix protein 1 (M1), but also requires the phosphorylation of NP, and to a minor extent, NEP, as well as the SUMOylation of M1 (17-19). C14orf166, despite its cellular origin, is also a key factor in the IAV life cycle, promoting vRNA replication and transcription (20). C14orf166 interacts with and activates the cellular RNA polymerase II and the PA subunit of the RdRp (21). Silencing C14orf166 expression results in a decrease in vRNA transcription, replication and production of the infectious virus (22). In addition to function as a transcriptional modulator, C14orf166 interacts with several proteins engaged in pre-mRNA processing, such as DDX1, suggesting it also serves a role in RNA maturation (23). Furthermore, it has also been demonstrated that C14orf166 binds to progeny vRNP in the cytoplasm, suggesting that it accompanies the newly-generated vRNP molecules during their export to the cytoplasm (24). In addition, it has been demonstrated that C14orf166 may be incorporated into IAV particles, tightly bound to vRNP, which promotes viral and cellular polymerase interaction for viral transcription (24).

3. Role in other viral infections

C14orf166 is also involved in other viral infections, where it serves similar roles as those described previously in IAVs (25-27). A previous study reported that C14orf166 interacts with a core protein of the hepatitis C virus (HCV), HCVc174 (25). This interaction appears to be relevant in acute and chronic HCV infection. In the nucleus, it has been suggested that the C14orf166/HCVc174 complex may lead to aberrant mitosis of infected hepatocytes, and result in hepatic carcinoma (25). In addition, the C14orf166/HCVc174 complex also interacts with cytoplasmic ninein molecules, essential for microtubule assembly and organization (25). This may facilitate viral entry and assembly, contributing toward more efficient establishment of the infection. In addition, C14orf166 also interacts with the nucleocapsid protein of infection with the bronchitis virus (26) and is involved in the nuclear steps of HIV-1 RNA metabolism (27).

4. Regulation of RNA metabolism

RNA metabolism is modulated by the interaction between RNA molecules and RNA-binding proteins. C14orf166 is involved in several steps of RNA metabolism, including RNA transcription, maturation and translation. C14orf166 interacts with several factors essential for RNA synthesis and processing, including transcription factor 4, heterogeneous nuclear ribonucleoprotein R, poly A binding protein 1 and the nuclear pore complex Nup153 (28-30). In addition, it has been demonstrated that C14orf166 acts as a shuttling protein for DDX1, HSPC117 and FAM98B (31). DDX1 is an RNA helicase that binds to homopolymeric poly(A) RNA and regulates HIV-1 replication (32,33), HSPC117 is an essential subunit of a tRNA splicing ligase complex (6), and FAM98B has been associated with colorectal cancer malignancy, but its physiological function remains unknown. As a shuttling protein, C14orf166 mediates the transport of the RNA molecules encoding these proteins between the nucleus and the cytoplasm. Notably, C14orf166 has demonstrated asymmetric kinetics in its nucleo-cytoplasmic movement, as it leaves the nucleus faster than it enters it (34). Reimportation of C14orf166, DDX1, HSPC117 and FAM98B requires active transcription, that is, initiation of the C14orf166-DDX1-HSPC117-FAM98B complex requires the synthesis of new RNA cargos (34). In addition, C14orf166 regulates the expression of these C14orf166-interacting proteins, as C14orf166-silencing leads to their nuclear and cytosolic downregulation (34). Further research is required to unravel how this complex is formed and its role in the regulation of the nuclear and cytosolic RNA fate.

The 5'end of mRNA molecules contains a 7-methyguanilate molecule connected to the RNA through a 5' to 5'triphosphate linkage. This structure protects mRNA molecules from degradation by ribonucleases and binds to initiation factors, including eIF4E triggering the translation of the messenger molecule. Recently, it has been reported that the complex C14orf166-HSPC117-DDX1-FAM98B may also bind to the cap structure independently to eIF4E (35). C14orf166 retained the ability to bind to the cap structure without its complex partners, although the binding affinity was markedly lower, suggesting that HSPC117, DDX1 and FAM98B enhance the cap-binding ability of C14orf166 (35). In addition, the same study reported that the C14orf166 complex may positively regulate the translation of specific mRNAs (35). Finally, in addition to the previously described roles in transcription and translation, C14orf166 is also involved in RNA maturation (36).

5. Role of C14orf166 in cancer

Cancer is a disease involving uncontrolled cell proliferation due to the cells' ability to escape the body's natural mechanism of cell death (37). The cancer mortality rate has markedly increased in recent years (37). Although great efforts have been made to decrease mortality and prolong the survival time of patients with cancer, this disorder remains a major threat to human health. The lack of specific and sensitive markers for early diagnosis is one of the major causes of a poor prognosis (37). Conventional treatments, including surgical resection of the tumor, chemotherapy or radiotherapy, often

Table I. Studies of C14orf166 in various types of carcinoma.

Carcinoma	Changing trend	Associated clinicopathological characteristics	Prognosis	(Refs.)
Brain tumor	Upregulated	-	-	(3)
Esophageal squamous cell carcinoma	Upregulated	T, N and M stage	Negative	(20)
Breast cancer	Upregulated	T, N and M stage, PR, survival time, vital status	Negative	(31)
Bladder cancer	Upregulated	T and N stage, histological differentiation, vital status	Negative	(38)
Nasopharyngeal carcinoma	Upregulated	Sex, clinical stage, T, N and M stage, vital status, treatment method	Negative	(39)
Uterine cervical cancer	Upregulated	FIGO stage, vital status, tumor size, M stage, serum squamous cell carcinoma antigen level	Negative	(40)
Pancreatic adenocarcinoma	Upregulated	N stage	Negative	(48)
Hepatocellular carcinoma	Upregulated	T, N and M stage, tumor size, serum AFP level, tumor recurrence	Negative	(49)

T, tumor; N, lymph node metastasis; M, distant metastasis; PR, progesterone receptor; FIGO, The International Federation of Gynecology and Obstetrics; AFP, α-fetoprotein; C14orf166, chromosome 14 open reading frame 166.

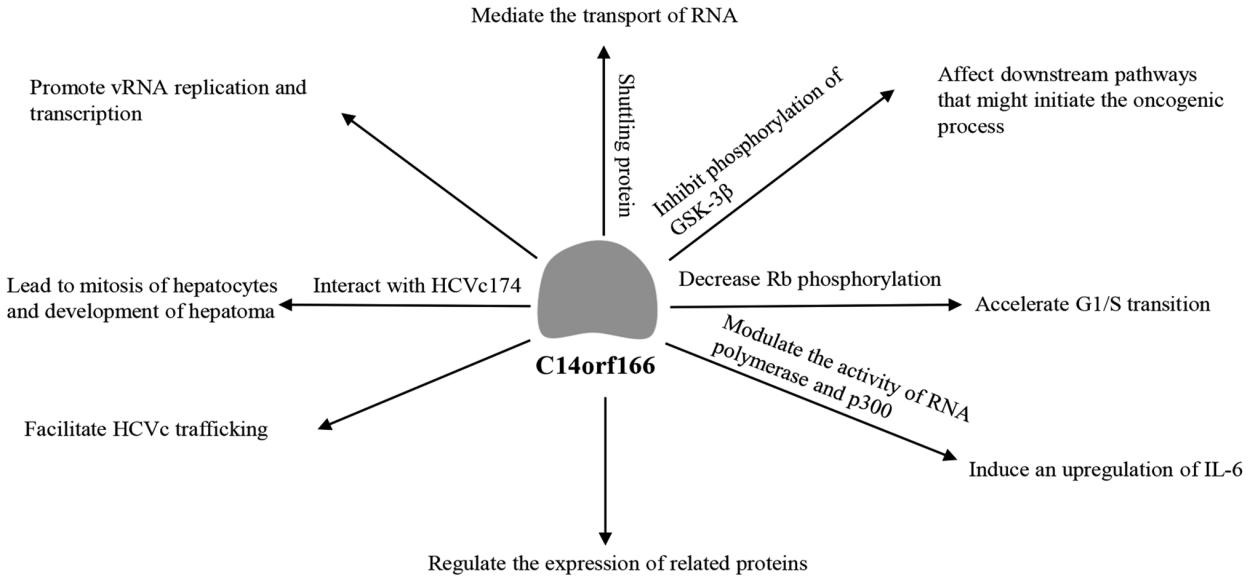

Figure 1. Effect of C14orf166 in viral infection, RNA metabolism and cancer. C14orf166, chromosome 14 open reading frame 166; vRNA, viral RNA; HCV, hepatitis C virus; Rb, retinoblastoma protein; GSK-3β, glycogen synthase kinase 3β.

have serious associated side effects, and reoccurrence of the cancer following the treatment is a common concern (37). In addition, tumors often develop resistance to chemotherapy drugs (31). Therefore, there is an urgent requirement to develop novel approaches for the diagnosis and treatment of cancer. Over the past 20 years, a large number of studies have reported a role for C14orf166 in cancer (Table I). C14orf166 is overexpressed in cancer tissue, compared with healthy tissue (Table I). In addition, high expression of C14orf166 is associated with shorter overall survival and disease-free survival times in various types of cancer (31,38-40). This suggested that C14orf166 levels in serum may be used as a prognostic factor and therapeutic target, encouraging further investigation to elucidate the pathological role that C14orf166 may serve (31,41,42). Howng *et al* (3) demonstrated that C14orf166 interacts with the C-terminal coiled-coil of centrosomal ninein suppressing the N-terminal phosphorylation by glycogen synthase kinase 3β (GSK-3β). GSK-3β is associated with cancer, as high GSK-3β expression levels are associated with the development of cancer (38). Additionally, GSK-3β may phosphorylate several substrates from the JAK2/STAT3, Wnt/β-catenin and PI3K-AKT-mTOR signaling pathways that mediate cancer initiation, progression and drug resistance (39,43,44). In addition, C14orf166 is a JKA2-interacting protein that activates JKA2/STAT3 signaling, which may lead to esophageal and cervical cancer (40,45). Although speculative, we hypothesize that C14orf166-ninein binding inhibits the ninein-GSK-3β and

the phosphorylation of GSK-3β, which affects downstream pathways that may initiate the oncogenic process. C14orf166 has also been reported to decrease retinoblastoma protein phosphorylation, accelerating G1/S transition in bladder and breast cancer cells and contributing toward uncontrolled proliferation, although the details of this mechanism have not yet been fully elucidated (31,41). Finally, C14orf166 has been demonstrated to modulate the activity of RNA polymerase and p300, inducing an upregulation of IL-6 (46). High levels of this cytokine are associated with poor prognosis (46) and promote continuous, unregulated signaling through STAT3 (47). Taken together, the results of these studies demonstrated that C14orf166 serves a critical role in the initiation and progression of cancer. Therefore, C14orf166 stands as a promising biomarker candidate and actionable drug target, and further research should be conducted to broaden our knowledge regarding its functions.

6. Conclusion

C14orf166 has been identified as a crucial protein during several virus infections, including IAV and HCV. In a physiological context, C14orf166 is a key factor for RNA transcription, maturation and translation. In cancer tissue, it is overexpressed and appears to contribute toward the uncontrolled cell proliferation. Therefore, it may be used as a diagnostic and prognostic biomarker for various types of cancer in the future, although there remain a number of questions that require addressing.

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Authors' contributions

QC conducted the literature search. RL proofread the manuscript. Both authors wrote, read and approved the final manuscript.

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Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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