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Targeting Cdc20 as a novel cancer therapeutic strategy

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ABSTRACT

The Anaphase Promoting Complex (APC, also called APC/C) regulates cell cycle progression by forming two closely related, but functionally distinct E3 ubiquitin ligase sub-complexes, APC^{Cdc20} and APC^{Cdh1}, respectively. Emerging evidence has begun to reveal that Cdc20 and Cdh1 have opposing functions in tumorigenesis. Specifically, Cdh1 functions largely as a tumor suppressor, whereas Cdc20 exhibits an oncogenic function, suggesting that Cdc20 could be a promising therapeutic target for combating human cancer. However, the exact underlying molecular mechanisms accounting for their differences in tumorigenesis remain largely unknown. Therefore, in this review, we summarize the downstream substrates of Cdc20 and the critical functions of Cdc20 in cell cycle progression, apoptosis, ciliary disassembly and brain development. Moreover, we briefly describe the upstream regulators of Cdc20 and the oncogenic role of Cdc20 in a variety of human malignancies. Furthermore, we summarize multiple pharmacological Cdc20 inhibitors including TAME and Apcin, and their potential clinical benefits. Taken together, development of specific Cdc20 inhibitors could be a novel strategy for the treatment of human cancers with elevated Cdc20 expression.

Contents

1. Introduction

Ubiquitination has been characterized to play a critical role in regulating diverse cellular processes including cell cycle progression, cell proliferation, apoptosis, DNA damage, migration and invasion (Hoeller et al., 2006; Nakayama & Nakayama, 2006). It has been well accepted that ubiquitination by the ubiquitin proteasome system (UPS) is a post-translational modification that controls protein degradation thereby the abundance of essential proteins involved in a plethora of cellular processes (Lipkowitz & Weissman, 2011; Bassermann et al., 2014; Z. Wang et al., 2014). A wealth of evidence has emerged that two related, multi-subunit E3 ubiquitin ligase enzymes, the Anaphase Promoting Complex (APC) and the Skp1–Cullin1–F-box complex (SCF) have been considered as the major driving forces governing cell cycle progression (Lau et al., 2012; Wang et al., 2012; J. Zhang et al., 2014; Z. Wang et al., 2014). Notably, APC is the most complex E3 ubiquitin ligase that consists of at least 14 subunits (namely, APC1/TSG24, APC2, APC3/Cdc27,

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APC4, APC5, APC6/Cdc6, APC7, APC8/Cdc23, APC10/Doc1, APC11, APC13/SWM1, APC15/Mnd2, APC16, and Cdc26) and either one of two co-activators, Cdh1 or Cdc20 (Foe & Toczyski, 2011; Schreiber et al., 2011; Chang & Barford, 2014). Due to its large size and complex nature, the structure of the full APC holoenzyme remained poorly understood until recently, when its structure was elucidated by the Cryo-electron microscopy technology (Kulkarni et al., 2013; Chang & Barford, 2014; Chang et al., 2014). These structural insights support the model that the APC consists of a scaffolding subunit (including APC1, APC4, APC5), a catalytic and substrate recognition subunit (APC2, APC11, APC10), a tetratricopeptide repeat arm (APC3, APC6, APC8), and an accessory subunit (APC13, Cdc26, APC16) (Fig. 1) (Vodermaier et al., 2003; McLean et al., 2011). Without a doubt, it is necessary to further determine the architectural details of the APC to aid in further understanding its biological functions.

To exert its biological functions, the APC core is associated with two activators, Cdc20 (cell division cycle 20 homologue, also called Fizzy) and Cdh1 (Cdc20 homologue 1, also known as Fizzy-related protein 1, FZR1), respectively, leading to two distinct E3 ubiquitin ligase complexes, APC^{Cdc20} and APC^{Cdh1} (Penas et al., 2011; Z. Wang et al., 2013). Cdc20 contains seven WD40 repeats that are necessary for mediating protein–protein interactions (Hartwell et al., 1973). Emerging evidence has also revealed that Cdc20 and Cdh1 control the substrate specificity of the APC core-complex to bind and ubiquitinate target proteins for subsequent degradation. Notably, it has been demonstrated that Cdc20 and Cdh1 recruit their substrates via different motifs. For example, APC^{Cdc20} typically targets its substrates which contain a Destruction-box (D-box) (Michaelis et al., 1997; Clute & Pines, 1999; Nasmyth, 2001), TEK (Jin et al., 2008) or the newly identified ABBA (Di Fiore et al., 2015) motifs (Table 1). On the other hand, APC^{Cdh1} largely recruits substrates with either KEN-box (McGarry & Kirschner, 1998; Petersen et al., 2000), D-box (McGarry & Kirschner, 1998; Petersen et al., 2000; den Elzen & Pines, 2001; Geley et al., 2001; Bashir et al., 2004; Lindon & Pines, 2004; Wei et al., 2004), A-box (Littlepage & Ruderman, 2002), O-box (Araki et al., 2003), CRY box (Reis et al., 2006), LLK (Gao et al., 2009) or GxEN box (Castro et al., 2003) motifs (Table 1). It is still not fully understood how APC^{Cdc20} and APC^{Cdh1} mechanistically recruit their substrates with different motifs, but it provides a possible molecular explanation for their distinct roles in tumorigenesis that might stem from their abilities in targeting a different spectrum of substrates for destruction.

Consistent with this notion, although both Cdc20 and Cdh1 can activate the APC E3 ligase, they have distinct biological functions (Yu, 2002; Clijsters et al., 2013). For example, APC^{Cdc20} exerts its function during the metaphase to anaphase transition through destruction of critical cell cycle regulators (Yu, 2007; Kim & Yu, 2011), whereas APC^{Cdh1} plays a key role in the late M and G1 phases (Qiao et al., 2010; Hu et al., 2011). Moreover, Cdh1 is considered as a tumor suppressor, while Cdc20 exhibits its oncogenic function (Penas et al., 2011; Z. Wang et al., 2013). It is known that Cdc20 is an essential developmental gene, whose disruption in mice caused embryonic lethality and displayed condensed chromosomes, in part due to aberrant mitotic arrest (Li et al., 2007). Consistently, ablation of endogenous Cdc20 blocks in vivo tumorigenesis in a skin-tumor mouse model induced by a two-stage carcinogenesis protocol, largely due to elevated cellular apoptosis (Manchado et al., 2010). Furthermore, depleting endogenous Cdc20 in various cancer cell lines also led to a mitotic arrest followed by cell death. Together, these studies suggest that inhibition of APC^{Cdc20} enzymatic activity might lead to an elevated cellular apoptosis. Although the exact molecular mechanism underlying Cdc20 loss-induced apoptosis remains unknown, these studies strongly argue for Cdc20 as a novel anti-cancer therapeutic drug target. Indeed, inactivating APC by an IR-mimetic inhibitor, pro-TAME, which targets both APC^{Cdc20} and APC^{Cdh1}, also induced cell death in multiple cancer cell lines (Zeng et al., 2010). Therefore, in this article, we summarize the oncogenic role of Cdc20 in a variety of human cancers including pancreatic cancer, breast cancer, prostate cancer, colorectal cancer, lung cancer, glioblastomas, bladder, hepatocellular carcinoma and other cancers. Moreover, we discuss how aberrant overexpression of Cdc20 in various types of human cancers could be used to guide the development and use of Cdc20 inhibitors for treating human cancers. Finally, we describe several Cdc20 inhibitors and their potential clinical benefits.

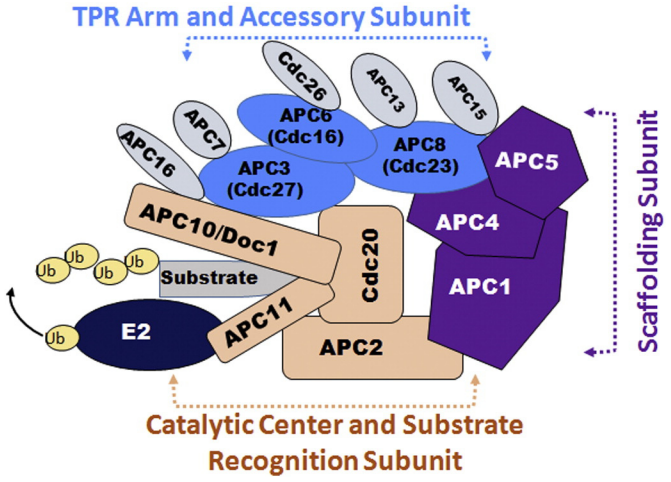

Fig. 1. A schematic illustration of the APC ubiquitin E3 ligase complex. The APC core complex includes a scaffolding subunit (APC1, APC4, APC5), a catalytic and substrate recognition subunit (APC2, APC11, APC10), a tetratricopeptide repeat arm (APC3, APC6, APC8), and an accessory subunit (APC13, Cdc26, APC16).

2. Cdc20 exerts its biological functions largely by targeting its downstream substrates for ubiquitination and subsequent degradation

In recent years, many downstream targets of Cdc20 have been identified by various groups (Table 2). The initial role of Cdc20 was elucidated primarily in regulating cell cycle progression after it was discovered nearly half a century ago (Hartwell et al., 1970). Cells with Cdc20 mutants blocked cell division and stopped cell cycle progression toward anaphase and chromosome segregation (Hartwell et al., 1970). Mechanistically, many identified substrates of Cdc20 are involved in mitotic procession including Securin (Zur & Brandeis, 2001), Cyclin B1 (Lim et al., 1998; Shirayama et al., 1999), Cyclin A (Ohtoshi et al., 2000; Geley et al., 2001), Nek2A (Hames et al., 2001), Cenp-F (Gurden et al., 2010) and p21 (Amador et al., 2007). Further studies implicated Cdc20 in governing cellular apoptosis through regulating the stability of Mcl-1 (Harley et al., 2010) and Bim (Wan et al., 2014). Interestingly, Cdc20 has also been reported to play a key role in ciliary disassembly (W. Wang et al., 2014) and brain development (Yang et al., 2007; Yang et al., 2009). In the following sections, we will summarize the different biological functions of Cdc20 in cell cycle progression, apoptosis, ciliary disassembly and brain development.

2.1. Regulation of cell cycle

Different from APC^{Cdh1} with major functions in late M and G1 phases, APC^{Cdc20} plays an indispensable role during the metaphase to anaphase transition by targeting critical cell cycle regulators including Securin (Michaelis et al., 1997; Nasmyth, 2001) and Cyclin B (Clute & Pines, 1999) for ubiquitination-mediated destruction. It has been also identified that Cdc20 binds p21 in a D-box motif-dependent manner to promote the timely degradation of p21 in prometaphase, whereas Skp2 degrades p21 during the G1/S transition (Amador et al., 2007). Another study also proposed that Cdc20-mediated degradation of conductin governs Wnt/β-catenin signaling and controls the cell cycle (Hadjihannas et al., 2012). In line with this finding, Cdc20-resistant