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Cycling for renewal: Cell cycle machinery maintains prostate cancer stem-like cells

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The Anaphase Promoting Complex/Cyclosome (APC/C) plays an indispensable role in regulating timely cell cycle transition from mitosis to G1 phase. APC/C is a multi-subunit ubiquitin E3 ligase that consists of at least 14 subunits. Two substrate-binding subunits, Cdc20 and Cdh1 (also named FZR1), recruit target proteins to the APC/C core enzyme for poly-ubiquitylation. Cdc20 and Cdh1 associate with the APC/C core complex at different cell cycle phases to ensure proper cell cycle progression. Cdc20 activates APC/C at metaphase/anaphase transition to promote the ubiquitylation of cyclin B and securin, which drives mitotic exit. Once cells enter G1, Cdh1 subsequently binds to APC/C and facilitates the ubiquitylation of a panel of M phase regulators including cyclins, mitotic kinases, as well as Cdc20.

Given the essential role of Cdc20 in governing M phase cell cycle progression, it is not surprising that genetic ablation of Cdc20 is embryonic lethal in mice [1]. Intriguingly, conditional deletion of Cdc20 in skin tumours led to tumour regression, suggesting a pro-survival role for Cdc20 in cancer cells [1]. Consistent with the notion that Cdc20 functions as a proto-oncogene, a wealth of genetic and histological evidence including the TCGA datasets unveiled that Cdc20 is highly expressed in many human malignancies, which include breast cancer, ovarian cancer, cervical cancer, lung cancer, and gliomas [2]. The pathophysiologic role of Cdc20 in carcinogenesis has been attributed to increased genomic instability due to premature mitotic exit and aneuploidy [3]. Furthermore, a number of studies highlighted an oncogenic role of Cdc20 by promoting the proteolysis of tumour suppressors such as $p21^{CIP1/WAF1}$ [4] and Bim [5]. However, it still remains largely elusive how mechanistically Cdc20 facilitates tumour initiation and progression.

In the current issue of *EBioMedicine*, Zhang et al. assessed the oncogenic function of Cdc20 in prostate cancer and uncovered a role for Cdc20 in maintaining the expression of stemness genes in prostate cancer cells [6]. Through analysing prostate tumour samples from a cohort of 121 patients, the authors found that high expression of Cdc20 is associated with advanced stages of prostate cancer with poor survival. Importantly, a positive correlation between Cdc20 and a cancer stem cell-like marker, CD44, was unveiled in this study. In addition to clinical samples, the authors also discovered a positive correlation between Cdc20 and CD44 expression in prostate cancer cell lines. Of note, the $Cdc20^{high}/CD44^{high}$ population of prostate cancer cell lines DU145 and C4—2B was enriched in 3D spheroids compared to adherent cultures. This population of cells was also found mainly in docetaxel-resistant cells rather than in naïve cells. Such findings are particularly interesting as previous report demonstrated that APC/C^{Cdc20} augments Sox2 transcriptional activity in glioblastoma stem-like cells [7]. Both discoveries support a potential role for Cdc20 in maintaining a stem cell-like cell population in human cancers.

In support of the pro-stemness function of Cdc20 in prostate cancer cells, depletion of Cdc20 by shRNA in $CD44^+$ prostate cancer cells led to a significant reduction of stemness gene expression including SOX2, KLF4, Myc, and OCT4. Moreover, 3D spheroid formation and in vivo xenograft tumour development were hampered upon Cdc20 depletion, and Cdc20-depleted $CD44^+$ prostate cancer cells were more vulnerable to docetaxel treatment compared to control cells.

To unravel the underlying mechanism(s), RNA-Seq analysis revealed that a set of β-catenin target genes were downregulated in Cdc20-depleted $CD44^+$ C4-2B cells. In support of this observation, depletion of β-catenin antagonized Cdc20-maintained stem cell-like features of $CD44^+$ prostate cancer cells. Since β-catenin stabilization and nuclear translocation is vital to the ignition of the Wnt signaling pathway, Zhang et al. found that Cdc20 indeed stabilized β-catenin and facilitated its nuclear localization. It was puzzling how Cdc20, being a ubiquitin E3 ligase subunit, acts to stabilize β-catenin. The authors followed the Wnt/β-catenin circuit and focused on the "destruction complex" that promotes β-catenin degradation. They unveiled that Cdc20 negatively regulates Axin1 protein abundance, and in turn inhibits β-catenin proteolysis. The discoveries report here by Zhang et al. support an oncogenic role of Cdc20 in prostate cancer, and thus suggest Cdc20 as a potential biomarker for a $CD44^+$ stem cell-like population in prostate tumours.

The Wnt signaling pathway has been closely associated with mitotic spindle function and chromosome segregation, Axin2, GSK3 and β-catenin are found in centrosomes during mitosis [8]. It is thus tempting to postulate that the interplay between APC/C^{Cdc20} and the Wnt/β-catenin cascade may govern mitotic progression, and that its aberrancy may contribute to cancer initiation. While accumulating evidence supports an oncogenic role of Cdc20 in tumourigenesis, the

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development of specific Cdc20 inhibitors is still in its infancy. At present, two strategies have been utilized to target APC/C^{Cdc20}: 1) by blocking APC/C-Cdc20 binding, e.g. tosyl-L-arginine methyl ester (TAME) [9]; 2) by blocking Cdc20-substrate interaction, e.g. Apcin [10]. It will be of great interest to evaluate the efficacy of these compounds in pre-clinical prostate cancer models. Furthermore, combinational targeting Cdc20 with chemotherapeutic agents or other targeted options will be attractive in follow-up studies.

Author disclosure

The authors declare no conflicts of interest.

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