INTRODUCTION
The cullin-RING ubiquitin ligases (CRLs) are the largest E3 ligase family in eukaryotes, and ubiquitinate a wide array of substrates involved in cell cycle, signaling, DNA damage response, gene expression, chromatin remodeling, and embryonic development. Cullins serve as elongated scaffolds that assemble functional E3 complexes by utilizing distinct adaptors to recruit substrate receptors for direct the degradation of proteins involved in a wide spectrum of cellular functions. Aberrant expression of the cullin 4A (CUL4A) gene is found in many tumor types, while mutations of the cullin 4B (CUL4B) gene are causally associated with human X-linked mental retardation. This focused review will summarize our current knowledge of the two CUL4 family members in the pathogenesis of human malignancy and neuronal disease, and discuss their potential as new targets for cancer prevention and therapeutic intervention.

The cullin 4-RING ubiquitin ligase (CRL4) family employs multiple DDB1–CUL4 associated factors substrate receptors to direct the degradation of proteins involved in a wide spectrum of cellular functions. This focused review will summarize recent findings that have shed light on the role of CUL4 activity in human disease.

CUL4A AND CANCER
CUL4A was initially identified as an amplified or overexpressed gene in primary human breast cancers (Chen et al., 1998). Genome-wide analysis of human cancers revealed CUL4A amplification in 5% of familial and sporadic breast cancers, and as high as 20% in the basal-like breast cancer subtype that is associated with aggressive growth and poor prognosis (Melchor et al., 2009). CUL4A amplification has also been found in squamous cell carcinomas (Shinomiya et al., 1999), adrenocortical carcinomas (Dohna et al., 2000), childhood medulloblastoma (Michiels et al., 2002), hepatocellular carcinomas (Yasui et al., 2002), and primary malignant pleural mesotheliomas (Hung et al., 2011). Recently, genome-wide high-density SNP arrays further revealed high CUL4A gene copy number in a subset of lung and ovarian carcinomas, as well as other solid tumor types (Beroukhim et al., 2010). Moreover, high CUL4A expression correlates with significantly shorter overall and disease-free survival (Schindl et al., 2007), indicating that dysregulation of CUL4A may play a role in promoting oncogenesis. Mouse models support this hypothesis, as skin-specific Cul4a knockout mice showed marked resistance to UV-induced carcinogenesis compared to wild-type and heterozygous mice (Liu et al., 2009). Transgenic mice with inducible expression of exogenous CUL4A developed pulmonary hyperplasia, which is consistent with a role for dysregulated CUL4A in driving uncontrolled proliferation (Li et al., 2011a). The role of CUL4B in carcinogenesis remains to be determined.
The damaged DNA binding proteins DDB1 and DDB2 were first characterized as DNA damage sensors that initiate the nucleotide excision repair (NER) pathway following UV irradiation (reviewed in Tang and Chu, 2002). Earlier studies identified the DDB1–DDB2 heterodimer as both a target and component of the CRL4 ubiquitin ligase complex (Shiyanov et al., 1999; Chen et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003). DDB2 mutations that impair the recognition of UV-induced DNA lesions are causal for the photosensitivity and early onset of skin cancer found in xeroderma pigmentosum group E (XPE) patients (Nichols et al., 2001; Nag et al., 2001; Groisman et al., 2003).
Table 1 | Involvement of CUL4A substrates in pathogenesis.

| DCAF   | Substrate | Substrate functions                                    | Associated pathogenesis                  | Reference                                                                 |
|--------|-----------|--------------------------------------------------------|------------------------------------------|----------------------------------------------------------------------------|
| DDB2   | DDB2      | Nucleotide excision repair; DCAF substrate receptor. | Xeroderma pigmentosum; skin cancer       | Nichols et al. (2000), Chen et al. (2001), Groisman et al. (2003), Nag et al. (2001), Sugasawa et al. (2005) |
| DDB2   | XPC       | Nucleotide excision repair                             | Xeroderma pigmentosum, skin cancer       | Sugasawa et al. (2005)                                                     |
| Cdt2   | p21/CIP/WAF1 | CDK inhibitor                                        | Normal cell cycle and DNA damage response | Abbas et al. (2008), Kim et al. (2008), Nishitani et al. (2008)             |
| Cdt2   | Cdt1      | DNA replication licensing factor                      | DNA re-replication                       | Higa et al. (2006a), Jin et al. (2006)                                     |
| Cdt2   | PR-Set7/Set8 | Histone methyltransferase                  | Unknown                                    | Abbas et al. (2010), Centore et al. (2010), Jorgensen et al. (2011), Oda et al. (2010), Tardat et al. (2010) |
| Fbw5   | Tsc2      | Inhibitor of mTOR signaling                         | Tuberous sclerosis                       | Hu et al. (2008)                                                           |
| β-TrCP | REDD1     | Inhibitor of mTOR signaling                         | unknown                                   | Katiyar et al. (2009)                                                     |
| RBBP7  | p150/Sai2  | Inhibitor of cell growth                             | Putative tumor suppressor                 | Sung et al. (2011)                                                        |
| TRCP4AP/TRUSS | N-Myc, C-Myc | Transcription factors | Oncoproteins, multiple tumors | Choi et al. (2010)                                                         |
| COP1   | c-Jun     | Transcription factor                                 | Oncoprotein, multiple tumors             | Wertz et al. (2004)                                                        |
| COP1   | p53       | Transcription factor                                 | Tumor suppressor                          | Dornan et al. (2004)                                                      |
| COP1   | ETV1      | Transcription factor                                 | Oncoprotein, prostate cancer              | Vitari et al. (2011)                                                      |
| DCAF1/VprBP | unknown  | Cell cycle regulator                                 | Oncoprotein, Inhibited by the             | Li et al. (2010)                                                           |
|         |           |                                                       | Merlin tumor suppressor                   |                                                                            |
| Cereblon | unknown  | Limb development/patterning                          | Terotogenic, multiple myeloma.           | Ito et al. (2010)                                                          |
| Unknown | HOXA9     | Transcription factor                                 | Inhibited by thalidomide                 |                                                                            |
| Unknown | p27/Kip1  | CDK inhibitor                                         | Acute myeloid leukemia                    | Zhang et al. (2003)                                                        |
| Unknown | cyclin E  | Cell cycle progression                                | Tumor suppressor                          | Higa et al. (2006b)                                                        |
| Unknown | Chk1      | Cell cycle checkpoint kinase                         | Oncoprotein, multiple tumors             | Higa et al. (2006b)                                                        |
|         |           |                                                       | Tumor suppressor                          | Zhang et al. (2005), Leung-Pineda et al. (2009), Guervilly et al. (2011) |

an actively dividing state (Sung et al., 2011), and RASSF1A (Jiang et al., 2011), a negative Ras effector that was previously identified as a target of the CRL1/SCF^Skp2^ (Skp1, CUL1, F-box-containing substrate receptor, and Rbx1) ubiquitin ligase (Song et al., 2008). Contrary to the trend of CUL4A-mediated degradation of tumor suppressors, the CUL4 substrate receptor TRCP4AP/TRUSS targets both N-Myc and C-Myc transcription factors for degradation (Choi et al., 2010). Stabilization of Myc protein in many cancer cell lines corresponds with TRCP4AP/TRUSS downregulation, indicating the potential significance of CUL4A-mediated post-translational regulation in restricting Myc protein levels. COP1, acting as a CUL4 substrate receptor, functions as a tumor suppressor by targeting the c-Jun proto-oncogene for ubiquitination (Wertz et al., 2004). However, tissue-specific differences have been reported in CRL4-independent COP1 ubiquitin ligase activity. The p53 tumor suppressor is targeted for degradation by COP1 (Dornan et al., 2004), which may provide mechanistic insight into COP1 overexpression observed in ovarian and breast cancer. Conversely, the oncogenic ETS transcription factors are also degraded in a COP1-dependent manner, and loss of COP1 activity results in ETV1 accumulation that promotes prostate epithelial cell proliferation (Vitari et al., 2011). Finally, ectopic expression of CUL4A in PC12 rat pheochromocytoma cells suppresses apoptosis and promotes cell survival (Tan et al., 2011), further indicating that CUL4A activity supports cell growth.

The oncogenic effects of CUL4A are highlighted by the finding that Merlin, a tumor suppressor encoded by NF2, inhibits the ubiquitin ligase activity of CUL4A in complex with VprBP/DCAF1 (Li et al., 2010). Moreover, mutations in Merlin that ablate the enzymatic inhibition of CRL4VprBP have been found in patients with the neurofibromatosis type 2 familial cancer syndrome (Li et al., 2010). VprBP silencing compromises tumorigenesis in Merlin-deficient mesothelioma cell lines, indicating the significance of CRL4VprBP signaling in promoting cellular proliferation (Li et al., 2010). Huang and Chen showed that Merlin was targeted for degradation by the CRL4VprBP ubiquitin ligase (Huang and Chen, 2008). However, Li et al. demonstrated that Merlin was not a substrate of CRL4VprBP, but rather served as a negative regulator of the CRL4VprBP ubiquitin ligase. Further biochemical and genetic studies are required to determine the functional relationship between Merlin and CRL4VprBP. VprBP is also required for cell cycle progression into S phase (Belzile et al., 2007; Fireck et al., 2007; Le Rouzic et al., 2007; Tan et al., 2007; Wen et al., 2007), but the mechanism of cell cycle regulation and the cellular targets of CRL4VprBP...
have yet to be determined. Nevertheless, these findings indicate a role for the CRL4VprBP ubiquitin ligase in promoting cell cycle progression and oncogenic transformation.

Despite the numerous growth-promoting pathways that are amplified by CUL4A activity, the degradation of other identified CUL4A substrates reveals a more complex effect on growth regulation. CUL4A plays a critical role in granulopoiesis by degrading the HOXA9 homeodomain protein, which may also restrict HOXA9-induced leukemogenesis (Zhang et al., 2003). The leukemogenic NUP98–HOXA9 fusion protein, which is derived from the t(9;11)(p15;p15) chromosomal translocation in acute myeloid leukemia patients, is resistant to CUL4A-mediated degradation, further indicating that CUL4A may play a role in the proper differentiation of hematopoietic cells (Chung et al., 2006). In addition to restricting the NER threshold, CRL4 also responds to DNA damage through histone H3 and H4 ubiquitination, which facilitates the recruitment of repair proteins (e.g., XPC) to damaged DNA (Wang et al., 2006). Thus, the CUL4A ubiquitin ligase may play distinct roles in tumorigenesis that are dictated by cellular context or environmental conditions.

CUL4B AND HUMAN X-LINKED MENTAL RETARDATION

CUL4B mutations in human patients have been found to be causal for X-linked mental retardation (XLMR) syndrome (Tarpey et al., 2007; Zou et al., 2007; Badura-Stronka et al., 2010; Isidor et al., 2010). Patient-derived cells also display increased camptothecin-induced topoisomerase I-dependent DNA breaks, which are associated with the peripheral neuropathy spinocerebellar ataxia with axonal neuropathy-1 (SCAN-1; Kerzendorfer et al., 2010). The unique CUL4B N-terminus may mediate the recruitment of distinct substrates for degradation, and their accumulation likely contributes to the CUL4B phenotype. WDR5, a subunit of the H3K4 methyltransferase complex, was initially identified as a DCAF and more recently characterized as a CUL4B substrate (Nakagawa and Xiong, 2011). XLMR-derived CUL4B mutations resulted in the accumulation of WDR5 and subsequent activation of neuronal genes that promote neurite extension. Peroxiredoxin III is another unique CUL4B substrate that may affect neural development through the regulation of reactive oxygen species (ROS) levels (Li et al., 2011b). Finally, the arylhydrocarbon receptor (AhR) acts as a unique CUL4B substrate receptor that targets estrogen and androgen receptors for proteasome-mediated degradation (Ohtake et al., 2007), further highlighting the role of CUL4B as a transcriptional regulator.

Distinct expression patterns may also account for the phenotypes observed in the Cul4b knockout mouse model. In addition to enhanced resistance against UV-induced skin carcinogenesis, Cul4a knockout also resulted in male infertility (Kopanja et al., 2011; Yin et al., 2011). These studies revealed non-overlapping expression patterns between CUL4A and CUL4B during the pachytene to diplotene stages in adult testes, thus accounting for the physiological requirement for CUL4A activity in spermatogenesis (Yin et al., 2011). The disease syndrome manifested in humans with CUL4B mutations may be attributed to exclusive substrate targeting and/or differential expression patterns of the CUL4 family members. In vivo interrogation of CUL4B activity using knockout mouse models would shed insight into the mechanism of pathology, and may identify avenues for therapeutic intervention.

CRL4 AS A CANDIDATE FOR THERAPEUTIC INTERVENTION

Manipulation of the post-translational stability of cellular proteins has been demonstrated to be a new and effective cancer therapeutic strategy. Proteasome inhibitors, such as bortezomib, non-specifically block the overall degradation of poly-ubiquitinated proteins, but preferentially sensitize rapidly dividing cells to apoptosis (Richardson et al., 2003; Kane et al., 2007; Orlowski and Kuhn, 2008). MLN4924, a small molecule inhibitor of the Nedd8 E1 activating enzyme, specifically blocks cullin activity, which leads to the accumulation of their substrates (Soucy et al., 2009). However, more precise targeting of CRL complexes has been shown to be possible with the discovery that the teratogenic agent thalidomide specifically inhibits Cereblon (CRBN) (Ito et al., 2010), an identified DCAF for the CRL4 ubiquitin ligase family. Substrates for CRL4CRBN have yet to be determined, but aberrant Fgf8 expression and signaling were observed following Cereblon inhibition (Ito et al., 2010). Thalidomide is currently used to treat multiple myeloma, indicating that Cereblon activity likely promotes cell growth.

Viral hijack of CRL4 activity may provide further insight into possible mechanisms of CRL4 intervention. Parainfluenza virus 5 (PIV5, formerly SV5) V protein binds DDB1, which recruits STAT2 to target STAT1 for ubiquitination and proteasome-mediated degradation, thus inhibiting the cellular interferon-induced response to viral infection (Precious et al., 2005, 2007). Additional rubulaviruses, such as human parainfluenza virus 2 and mumps virus, also target STAT proteins for degradation by redirecting DDB1 activity through their V proteins (Ulane and Horvath, 2002). DDB1 binding by the hepatitis B virus X protein (HBx) resulted in S phase arrest (Martin-Lluesma et al., 2008), and the subsequent deleterious effects contributed to hepatocellular carcinomas in a cell-non-autonomous manner that was recapitulated in hepatocyte-specific Ddb1 knockout mice (Yamaji et al., 2010). S phase arrest is also triggered by HIV-1 Vpr and HIV-2 Vpx proteins through CRL4VprBP binding, which may promote macrophage infection (Sharifi et al., 2012). Thus, the modification of DDB1 substrate binding represents another method of altering CRL4 activity for therapeutic purposes.

CONCLUDING REMARKS

Despite the significant sequence conservation and functional redundancy of the CUL4 family members, CUL4A and CUL4B play strikingly diverse roles in human disease. CUL4A activity promotes oncogenesis, as demonstrated by the overexpression and/or amplification of CUL4A in several tumor types and the resistance to UV-induced skin carcinogenesis in the Cul4a knockout mouse model, while loss-of-function mutations in CUL4B are causal for human X-linked mental retardation syndrome. Surprisingly, gene-trapped inactivation of Cul4b in mice resulted in embryonic lethality (Cox et al., 2010). The genetic interrogation of CUL4B awaits the generation of a conditional Cul4b knockout mouse model to identify the unique in vivo contributions of CUL4B activity, and the major substrates that are responsible for CUL4B-dependent disease phenotypes. Furthermore, additional mouse
models are required to gain a comprehensive understanding of the role of CRL4 in pathogenesis through the functional delineation of the DCAF substrate receptors, their substrates (Emanuele et al., 2011), and the associated cellular pathways whose dysregulation contribute to pathogenesis.

CUL4A represents an ideal target for therapeutic intervention, as genetic ablation in mice resulted in a marked resistance to carcinogenesis. Additionally, the recent structural determination of CRL4 assembly and activation provides a molecular platform for the design of inhibitors (Angers et al., 2006; Li et al., 2006; Fischer et al., 2011). Although the extensive protein–protein interface between CUL4 and DDB1 may present a formidable challenge for direct intervention by small molecule inhibitors, allosteric inhibitors are an attractive alternative to attenuate CRL4 activity, especially given the stringent requirements of proximity and E2–E3 orientation for effective ubiquitin transfer. Finally, the striking efficacy of thalidomide in treating multiple myeloma and its inhibition of Cereblon activity indicate that developing specific inhibitors for multiple subunits or interfaces, e.g., DCAF binding to either CRL4 or substrates, may prove to be feasible therapeutic strategies.

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