Potential of *DEK* proto-oncogene as a prognostic biomarker for colorectal cancer: An evidence-based review

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Abstract. Given its role in tumorigenesis and its correlation with various pathologic features of colorectal cancer (CRC), DEK is considered to have the potential to predict CRC prognosis. This review attempts to summarize current knowledge and evidence supporting the potential of DEK as a prognostic biomarker of CRC. We searched meta-analyses, systematic reviews, cohort studies, and cell line studies published in the last 10 years. A literature search was conducted in PubMed, Pubmed Central (PMC), Proquest, EBSCOHost, Scopus, and Cochrane Library using the keywords 'colorectal/colon/rectal cancer', 'DEK', 'biomarker', and 'prognosis'. Studies that were not published in English, without accessible full text, unrelated to clinical questions, or conducted with a design unsuitable for the eligibility criteria were excluded. Seven included studies reported the potential of DEK as a prognostic biomarker of CRC and its role in cancer cell proliferation, invasion, and metastasis. This role is achieved through the Wnt/β-catenin pathway, prevention of apoptosis through destabilization of p53, and bridging inflammation and tumorigenesis through the nuclear factor (NF)-κB pathway, causing chronic inflammation and activation of tumorigenic genes. DEK overexpression is also associated with CRC clinical and pathological features, such as tumor size, lymph node metastasis, serosal invasion, differentiation, tumor staging, and epithelial-mesenchymal transition. DEK overexpression was found to be associated with lower survival and recovery rates. Its prognostic value was comparable with other prognostic biomarkers of CRC, such as BRAF, topoisomerase-1, and CEA. A cohort study reported that DEK overexpression was associated with a better response to fluoropyrimidine-based chemotherapy, while a cell-line study indicated a correlation between DEK overexpression with a worse response to irinotecan-based chemotherapy. In conclusion, considering its correlation with CRC pathology, its association with worse CRC patient survival, and its possibility to forecast the therapeutic response of various chemotherapeutic regimens, DEK has the potential to be used as a CRC prognostic biomarker.

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Contents

1. Introduction

Approximately 1.9 million new cases of colorectal cancer (CRC) are diagnosed worldwide each year, and 935,000 CRC patients died of the disease in 2020. In Asia, based on the Global Cancer Incidence, Mortality, and Prevalence (GLOBOCAN) estimates of cancer incidence in 2020, there were 0.96 million cases of CRC, ranked second among all types of cancer, and mortality reached 0.46 million, ranked fourth among all cancer types (1). CRC has a poor prognosis that depends on the stage of the tumor. Data from the US Surveillance, Epidemiology, and End Results (SEER) Program revealed that the 5-year relative survival rate for stage I colon cancer is 92%. It decreases in stage IV CRC, to only 12%. Meanwhile, the 5-year relative survival rate for rectal cancer is likely lower, 88% for stage I and 13% for stage IV (2). The prognosis of CRC is related to its invasion, progression, or treatment effects (3). Pathological examination plays a vital role in therapeutic decision-making and disease prognosis.

The Tumor-Node-Metastasis (TNM) staging system, developed by the Union for International Cancer Control (UICC) and American Joint Committee on Cancer (AJCC), is one of the most common staging systems used in clinical

practice (4,5). The system is also used as a reference by some pathology reporting standards, such as the International Collaboration on Cancer Reporting (ICCR) (6) and the Korean Society of Pathologists (7). However, this method remains problematic since patients with the same tumor stage could have significant variations in histopathological features, such as tumor budding, invasion of the vascular and perineural tissue, tumor grade, and regression levels (5). Controversies in CRC pathology reporting also exist, including the subjective nature of some elements assessed, low reporting accuracy and reproducibility, and the lack of standard protocols (5,8). In addition, there are no established biomarkers available on conventional histopathological prognosis of CRC that can predict the risk of cancer recurrence, metastasis, resistance to chemotherapy, prompt targeted therapy, and survival (8).

The best biomarkers should support determining CRC staging for clinical use. Biomarkers are biological entities that detect the existence or progression of certain diseases or the effects of treatments. Biomarkers should have several important characteristics, such as high diagnostic accuracy, safety, easy measurements, value to establish an accurate diagnosis, and capability to narrow down treatment options (9). One of the advantages of using biomarkers is that tests become more accessible and less invasive and can be more accepted as part of a routine clinical examination (10). Thus, identifying new prognostic biomarkers in CRC is essential to identify changes that allow us to predict the prognosis of individual tumors to develop targeted treatments for better clinical outcomes.

DEK is a gene found in the structure of human genetic material and described as a transcription factor that is overexpressed in several neoplasms, including CRC. Functionally, *DEK* is involved in DNA repair, suppressing cellular aging, inhibiting apoptosis, and encouraging differentiation, which is involved in chronic inflammatory pathways and tumorigenesis (11). Related to its role in tumorigenesis and its correlation with some pathologic features of CRC, *DEK* is considered to have the potential for predicting CRC prognosis. This review aims to summarize current knowledge and pieces of evidence supporting the potential of *DEK* proto-oncogene as a prognostic biomarker of colorectal cancer.

2. Methods

In writing this evidence-based review, we developed a searching strategy using the PIO approach (Population: CRC patients or experimental cell models; Importance/intervention: pathological examination using the novel DEK biomarker; and Outcome: prognostic factor) to obtain studies examining the potential of DEK as a prognostic factor of CRC (12,13). We did not use comparison as there was no study with a direct comparison between DEK and previously established biomarkers for CRC. We used scientific databases such as PubMed, Pubmed Central (PMC), Proquest, EBSCOHost, Scopus, and Cochrane to obtain evidence with combined consecutively ordered keywords according to the disease-determinant-outcome (DDO) approach, 'colorectal/colon/rectal cancer' as the disease, 'DEK' and 'biomarker' as the determinant, and 'prognosis' as the outcome.

Articles included in this review are in the level of evidence 1 to 5 according to the Oxford Centre for Evidence-Based Medicine (CEBM) guidelines (14), written in English, and published in the last 10 years. We excluded non-English studies that were not accessible in full text, did not match the relevant study design criteria and did not follow with clinical questions. In the final review, we included meta-analysis, systematic review, and cohort studies published after January 2012 (a 10-year study period). We also included non-clinical studies highlighting the role of DEK in tumorigenesis and CRC prognosis.

3. Results

We obtained seven main articles, comprising a meta-analysis of cohort studies (level of evidence 1) (15), two cohort studies (level of evidence 2) (16,17), one cohort study combined with a non-clinical study (level of evidence 2) (18), and three non-clinical studies using CRC cell lines as bench research for DEK (level of evidence 5) (19-21). One of these studies, a cell line study, was discovered through hand-searching. As summarized in Table I (15-21), generally, existing evidence suggests that DEK is linked with worse clinicopathological characteristics and survival rates, especially in patients with specific genotypes [i.e., wild-type Kirsten rat sarcoma viral oncogene (*KRAS* oncogene) genotype]. Cell line studies indicate that high DEK expression is linked to the ability of cancer cells to avoid apoptosis, and DEK degradation might be decreased due to mutations leading to tumorigenesis. Lower expression of DEK is also related to a lack of epithelial-mesenchymal transition (EMT) and more infiltrative cancer. Lower DEK might suggest better therapy response with irinotecan-based chemotherapy regimens (with a biomarker, annexin A5, being increased). In contrast, in patients with stage II-III rectal adenocarcinoma, increased DEK is linked to better treatment response when fluoropyrimidine-based (FOLFIRI or 5-FU) chemotherapy regimens are used, due to a link with the pro-apoptotic factor p38.

The role of DEK as a biomarker for colorectal cancer prognosis: Non-clinical studies. Martinez-Useros *et al* (18) recorded that all CRC cell lines used in the research as samples were found to have overexpression of DEK protein. On the other hand, they also observed that when *DEK* gene expression was suppressed, especially in the representative cell lines DLD-1 and SW620, the ability of CRC cells to survive or migrate was significantly decreased. The suppression of *DEK* gene expression was found to cause slightly increased expression of annexin A5, a protein associated with cell apoptosis, and a significant simultaneous decrease in cell viability. However, a cell culture given 7-ethyl-10-hydroxycamptothecin (SN38), an active component of irinotecan, showed a significant ($P<0.05$) increase in expression of annexin A5 after experiencing suppression of DEK. These findings in both cell lines (DLD-1 and SW620) indicate the potential of DEK as a response marker to irinotecan-based chemotherapy in patients of CRC. This effect was not observed in cell cultures given 5-FU or LOHP (an active component of oxaliplatin). Cells with low DEK expression also were shown to have decreased Ki-67 index levels alongside increased production of cleaved caspase-3 (18).

A study by Lin *et al* (21) in 2014 discovered a significant positive relationship between the expression of the

Table I. Summary of the findings of DEK as a prognostic factor for CRC (15–21).

No.	Authors (ref), year	Design	LoE	Sample	Classification of positive DEK expression	Findings
1.	Liu *et al* (15), 2017	Meta-analysis	1	14 cohort studies, 8 of which cover cancers of the digestive system	N/A (meta-analysis)	DEK overexpression was significantly attributed to worse overall cancer survival, with low heterogeneity overall: i) All type of cancer: HR 1.70, 95% CI: 1.48-1.96, P<0.001 (I^2=9%, P=0.36) ii) Cancers of the digestive system : HR 1.83, 95% CI: 1.52-2.19, P<0.001 (I^2=18%, P=0.30)
2.	Martinez-Useros *et al* (17), 2018	Cohort study	2	74 stage II-III rectal adenocarcinoma patients undergoing neoadjuvant chemoradiotherapy using FOLFOX (n=14) or 5-FU (n=60)	Based on expression rating methods used for DEK in the Human Protein Atlas	High expression of DEK was associated with the possi bility of better neoadjuvant fluoropyrimidine-based chemotherapy response (P=0.023)
3.	Martinez-Useros *et al* (18), 2014	Cohort study	2	67 stage IV CRC patients treated with FOLFIRI regimen of chemotherapy	DEK intensity is based on a HistoScore calculating cellular antigen intensity and the number of positive cells. The intensity cutoff was not described	i) Progression-free survival was shorter in patients with higher DEK expression. However, the correlation between DEK and progression-free survival was only found in the *KRAS*^{wt} patient group (P<0.05) ii) The risk of progression was higher in *KRAS*^{wt} patients with increased expression of DEK (HR 2.4, 95% CI: 1.04-5.58, P=0.04)
		Experimental study	5	9 human-derived CRC cell lines, especially DLD-1 and SW620		iii) There was a higher DEK expression in CRC cell lines than in normal cells, especially in metastasis-derived cell lines iv) *DEK* silencing was correlated with a decrease in, viability delay of cell repair, a reduction in migrating ability, and better response to irinotecan-based chemotherapy (P<0.05) v) The difference in DEK expression did not correlate with a better response to 5-FU or oxaliplatin

Table I. Continued.

No.	Authors (ref), year	Design	LoE	Sample	Classification of positive DEK expression	Findings
4.	Lin *et al* (16), 2013	Cohort study	2	109 CRC patients	Positive for DEK: 5-25% positive cells Strongly positive for DEK: >25% positive cells	i) The proportion of positive and strongly positive DEK expression was significantly higher in cancer tissue of CRC patients than in normal tissue surrounding cancer in those same patients or patients with adenoma (P<0.01). (Positivity rate: 95.41 vs. 33.03 vs. 32.69%, strong positivity rate: 48.62 vs. 9.17 vs. 13.46%) ii) Proportion of patients with DEK overexpression was higher in group of patients with larger tumor size [OR 2.353 (95% CI: 1.086–5.101), P=0.029], moderate to poor differentiation [OR 2.824 (95% CI: 1.291–6.177), P=0.009], lymph node metastasis [OR 2.975 (95% CI: 1.360–6.509), P=0.006], invasion of serosal layer [OR 2.353 (95% CI: 1.072–5.163), P=0.031], and worse staging [OR 2.744 (95% CI: 1.261–5.971), P=0.010] iii) Proportion of patients with DEK overexpression was higher but not statistically significant in patients with male sex [OR 2.461 (0.924–6.556), P=0.067], older age ≥49 years [OR 1.298 (0.611–2.756), P=0.497], location on rectal compared to colon/ileocaecal [OR 0.900 (0.424–1.910), P=0.784], and increased CEA [OR 0.610 (0.273–1.362), P=0.228] iv) Patients with DEK overexpression had lower 5-year survival and lower disease-free survival (P<0.001) v) The lower survival rate was also found in patients with DEK overexpression coexisting with the appearance of one of four characteristics of aggressive CRC: serosal invasion, metastasis of the lymph nodes, worse staging, or higher CEA levels (P<0.001) vi) Overall, the median survival of patients in this study was 56 months; however, there was no specific information regarding the comparison of median survival in each subpopulation vii) DEK overexpression was an independent prognostic factor of CRC (HR 1.805, 95% CI 1.208–2.699, P=0.004)

Table I. Continued.

No.	Authors (ref), year	Design	LoE	Sample	Classification of positive DEK expression	Findings
5.	Lin *et al* (21), 2014	Experimental study	5	55 CRC patient tissue specimens, 22 standard colon mucosal specimens, 18 colorectal adenoma specimens	Positive for DEK: 5-25% positive cells Strongly positive for DEK: >25% positive cells	i) DEK protein expression was positively correlated to the Ki-67 index (P=0.030) but negatively correlated to the apoptosis index (P=0.010) ii) *DEK* silencing inhibited tumor cell growth and its ability to form colonies while contributing to a higher apoptosis rate iii) *DEK* silencing stimulated the *p53*/MDM2 pathway and Bcl-2/Bax pathways, and caspase-dependent pathways. All three contributed to a pro-apoptotic cell milieu
6.	Babaei-Jadidi *et al* (20), 2011	Experimental study	5	Human and mouse cell lines	An ordinal score scale of 1 (low) to 4 (extremely intense) was used to classify IHC for DEK	i) High expression of DEK was found in gut-specific *Fbxw7*-deleted intestine mouse tissue. The increased expression of DEK was also correlated with cells with mutated *Fbxw7* (P=0.001) ii) *DEK*-silenced cells were found to have more cells in the G0/G1 phase of the cell cycle and fewer cells in the S or M stage. In contrast, cells with high expression of DEK had more cells in S, G2, or M phase (P<0.05) iii) *Fbxw7* deactivated DEK by E3 ligase activity in the pres ence of GSK-3β
7.	You *et al* (19), 2017	Experimental study	5	Human-derived CRC cell lines, especially SW620 and SW480	DEK positivity was analyzed through western blot analysis as 'positive' or 'negative'	i) *DEK* silencing was significantly associated (P<0.05) with decreased expression of IMP3, increased E-cadherin, and decreased vimentin and MMP-9 ii) *DEK* silencing was significantly associated (P<0.05) with a drastic decrease in cell viability, the elevation of apop tosis rate, and decreased ability of cell invasion (accompanied by cellular transformation from interstitial-like spindle cells into epithelioid cells) iii) *DEK* silencing was not only associated with increased apoptosis (related to *p53* activity) but also EMT

Bcl-2/Bax, B-cell lymphoma 2 protein/Bcl-2-associated X protein; CEA, carcinoembryonic antigen; CI, confidence interval; CRC, colorectal cancer; EMT, epithelial-mesenchymal transition; *Fbxw7*, F-box/WD repeat-containing protein 7; FOLFIRI, calcium folinate-5-fluorouracil-irinotecan chemotherapy regimen; FOLFOX, calcium folinate-5-fluorouracil-oxaliplatin chemotherapy regimen; 5-FU, 5-fluorouracil; GSK-3β, glycogen synthase kinase-3β; HR, hazard ratio; Ki-67, the marker of proliferation Ki-67 protein; *KRAS*, Kirsten rat sarcoma virus protein; LoE, Level of evidence; p53/MDM-2, phosphoprotein p53/mouse double minute 2 homolog protein; MMP-9, matrix metalloproteinase-9.

DEK protein and Ki-67, a protein encoded by the *MKI67* gene associated with cell proliferation. The reverse correlation was found between DEK expression and apoptosis (lower DEK expression means higher apoptosis count, and vice versa). Transfection of silencer RNA for *DEK* (siDEK) also significantly decreased cell growth of the SW620 CRC cell line due to increased early apoptosis. In addition, DEK suppression also decreased mutant p53, MDM2, and Bcl-2 expression while upregulating Bax expression. Caspase-dependent apoptosis pathways were also found to be upregulated in cells with low DEK, as suggested by lowered expression levels of cleaved caspase-3 and caspase-9, but unaltered levels of caspase-8 and increased levels of cleaved poly-ADP ribose polymerase (PARP). These findings indicate that DEK suppression also suppresses pathways related to apoptosis, such as p53/MDM2, Bcl-2/Bax, and caspase-dependent pathways of apoptosis.

Babaei-Jadidi *et al* (20) noted that in the intestines of mice with mutations of the *Fbxw7* gene locus, a known tumor-suppressor locus, tumorigenesis was observed accompanied by changes in the expression of several proteins and genes, including DEK and RNA tropomyosin. Additionally, some data showed an association between DEK accumulation and the oncogenicity of the *Fbxw7* mutation, both in human and murine intestines. This association might elucidate the mechanism allowing DEK to cause tumorigenesis in CRC. Although the DEK transcription level did not change, mutations related to CRC tumorigenesis affected the DEK degradation process.

A study by You *et al* (19) using the SW480 and SW620 CRC cell lines testing the impacts of *DEK* knockdown with a DEK-interfering lentivirus showed decreased expression of DEK and insulin-like growth factor II mRNA binding protein 3 (IMP3), as well as changes in proteins associated with epithelial-mesenchymal transition (EMT); E-cadherin was significantly increased, along with a significant decrease in vimentin and matrix metalloprotein-9 (MMP-9). DEK downregulation was also associated with decreased cell viability, promotion of apoptosis, and decrease of cell invasion, which was related to the enhancement of E-cadherin and downregulation of vimentin and MMP-9.

The potential of DEK as a biomarker for colorectal cancer prognosis: Clinical studies. A meta-analysis by Liu *et al* (15) examined 14 cohort studies of DEK in cancers of various origins, eight of which were digestive system cancers. The study found that DEK overexpression was significantly attributed to worse survival of all types of cancer, including cancer of the digestive system. In cancers of all origins, overall survival of cases with DEK overexpression was lower compared to cases without DEK overexpression, either in univariate [n=13, hazard ratio (HR) 1.83, 95% confidence interval (CI): 1.64-2.05, P<0.001 (I^2=0%, P=0.71)] or multivariate analysis [n=9, HR 1.70, 95% CI: 1.48-1.96, P<0.001 (I^2=9%, P=0.36)]. The same finding was also reported in the subpopulation with cancers of the digestive system, either in univariate [n=8, HR 1.87, 95% CI: 1.62-2.15, P<0.001 (I^2=0%, P=0.69)] or multivariate analysis [n=6, HR 1.83, 95% CI: 1.52-2.19, P<0.001 (I^2=18%, P=0.30)]. All results of this meta-analysis have low to no heterogeneity.

A cohort study by Martinez-Useros *et al* (18) reported findings in a 67 stage IV CRC cohort receiving FOLFIRI, a chemotherapy regimen comprising folinic acid, 5-FU, and irinotecan. They revealed that progression-free survival was shorter in patients with higher DEK expression. By univariate Cox analysis, they reported significantly lower progression-free survival of CRC based on DEK status (HR 2.825, 95% CI: 1.238-6.449; P=0.014), while the progression-free survival of CRC based on BRAF (HR 1.119; 95% CI: 0.410-3.055; P=0.828) and topoisomerase-I status (HR 1.017; 95% CI: 0.364-2.845, P=0.974) was found to be insignificant. However, the correlation between DEK and progression-free survival was only found in the KRAS-wild-type ($KRAS^{wt}$) patient group (P<0.05). In contrast, this correlation was not observed in KRAS-mutated ($KRAS^{mut}$) patients. They also documented that the risk of progression was quantitatively higher in $KRAS^{wt}$ patients with increased DEK expression (HR 2.4, 95% CI: 1.04-5.58, P=0.04). Therefore, according to this study, CRC patients with $KRAS^{wt}$ and higher DEK expression have a poorer prognosis.

The same authors (17) also conducted another study in a cohort of 74 stages II-III rectal adenocarcinoma patients undergoing neoadjuvant chemoradiotherapy using FOLFOX, a chemotherapeutic regiment comprising folinic acid, 5-FU, and oxaliplatin (n=14), or 5-FU only (n=60). They observed that high expression of DEK was associated with the possibility of better neoadjuvant fluoropyrimidine-based chemotherapy response. In patients with an increased expression of DEK, 19% were found to have a complete reaction to neoadjuvant chemoradiotherapy. In contrast, no patient with low expression of DEK reached complete response (P=0.023). Although this appears to contradict the previous study, the authors argue that this occurs because the characteristics of the patients (including tumor type and stage) are different; thus, the potential for DEK as a cancer biomarker could be varied. In the previous study, annexin A5 expression was unchanged precisely in cell lines given 5-FU or the oxaliplatin active component LOPD (18). They explained that, in this situation, the association of DEK with the p38 pro-apoptotic factor might contribute to a better therapeutic response in patients (17). In addition, the high expression of DEK was possibly correlated to lower residual tumor cell burden after neoadjuvant chemoradiotherapy (22).

Lin *et al* (16) documented significant overexpression of DEK protein in CRC tissues compared to colorectal adenoma tissue or normal tissue. Positive expression for DEK was noted in 104 of 109 samples (95.41%) of CRC tissue specimens in the cohort, compared to 36 in adjacent normal tissue mucosa (33.03%) or 17 in 52 specimens of colorectal adenomas (32.69%). A strong expression was also found in favor of CRC specimens (52/109, 48.62%) compared to adjacent normal colon mucosa (10/109, 9.17%) or colorectal adenomas (7/52, 13.46%). All the results were statistically significant (P<0.05).

The same study (16) also documented a significant association between several clinicopathological characteristics related to worse CRC and overexpression of DEK, such as tumor size, lymph node metastasis, grades of differentiation, clinical cancer stage, and serous layer invasion. However, other characteristics showed no relationship with DEK overexpression, such as age, sex, tumor location, and carcinoembryonic antigen (CEA) level. It was also noted that CRC patients with serosal invasion, lymph node metastasis, increased CEA levels, and late-stage tumors with DEK overexpression respectively

had significantly (P<0.01) lower 5-year survival rates than their counterparts without DEK overexpression. Multivariate analysis using the Cox proportional hazards model discovered serosal invasion (HR 1.708, 95% CI: 1.414-2.555, P=0.009), late-stage disease (HR 1.663, 95% CI: 1.081-2.558, P=0.021), and DEK overexpression (HR 1.805, 95% CI: 1.208-2.699, P=0.004) as independent predictors of poor survival in CRC. Another known prognostic biomarker of CRC, CEA, was insignificant (HR 1.415; 95% CI: 0.904-2.214, P=0.129).

4. Discussion

The DEK proto-oncogene. The *DEK* proto-oncogene is a gene found in the structure of human genetic material. This gene is located at the chromosomal locus 6p22.3. It encodes a protein not currently categorized in any protein family and comprises 375 amino acids with an estimated weight of 43 kilodaltons (kDa) (16,23,24). The DEK protein has two DNA binding domains, namely the SLAM-associated protein (SAP) domain, found in several other proteins, and other DNA binding structures located in its carboxy-terminal region (24-26). Although its exact role is still being explored today, this protein is strongly suspected of being a regulator of the structure of genetic material, rather than of genetic sequences, where the SAP domain plays a role in triggering positive supercoiling of reversible DNA. The other DNA binding structures found in this protein can regulate the affinity of this protein for DNA, which can influence the transcription of genetic material (24-27). Moreover, the DEK protein was also documented to have a role in DNA replication and RNA splicing (28-30).

The *DEK* gene was initially investigated in acute myeloid leukemia (AML) patients, where it fused with the CAN protein/nucleoporin 214 (CAN/NUP214) gene on t(6; 9) (p23; q24) translocation. This gene translocation is even considered a basis for the stratification of AML patients (16,28). Although chromosomal changes in the *DEK* locus are not typical features of various malignant cases, there is a higher expression of DEK protein in different malignancies. Some types of malignancies that show increased expression of DEK include AML, hepatocellular carcinoma, glioblastoma, cervical cancer, ovarian cancer, melanoma, and others, including CRC (20,28,31-36).

The role of DEK in tumorigenesis and pathogenesis of colorectal cancer. Several studies on DEK have unraveled clues on how DEK plays a role in tumorigenesis in general and the pathogenesis of CRC. DEK can control several signaling pathways associated with cell proliferation, apoptosis, and inflammation, as shown in Fig. 1 (11,21).

DEK can influence cell proliferation by affecting the expression of several molecular signaling pathways, such as Wingless-related integration site/β-catenin-1 (Wnt/β-catenin). DEK can adjust Wnt molecular signaling pathways, including Wnt4, Wnt7b, and Wnt10b. These three Wnt pathways, known to affect cell proliferation and oncogenic cell phenotype, trigger β-catenin activation. Activation of β-catenin supports carcinoma proliferation, invasion, and metastasis (37,38).

Some studies have also demonstrated the ability of DEK to prevent apoptosis. One mechanism that allows this to happen is the destabilization of the gene *TP53* producing the tumor suppressor protein p53, which plays a role in responding to stress experienced by cells. Destabilization of p53 causes its function as a tumor suppressor to cease, triggering tumorigenesis. In the condition that DEK is suppressed, the role of p53 as a tumor suppressor can be carried out through the activation of p53 target genes, one of which produces the Bcl2-associated X protein (Bax). Activation of Bax, a pro-apoptotic factor commonly expressed on cell membranes, causes Bax to beome an integral protein in the mitochondrial membrane. Bax then triggers the release of apoptotic factors from the mitochondria, which further triggers cytochrome *c* and initiates a cascade reaction from caspase enzymes. This chain reaction triggers apoptosis (21,39).

Some literature suggests the relationship between inflammatory processes and tumorigenesis (40,41), and DEK was shown to have a role in bridging these two events. It is postulated that different pathways induce DEK overexpression in inflammatory and proliferative situations. Molecular pathways that trigger DEK overexpression in inflammatory conditions include AP-1, Ets-1, NFB, NF-AT, STAT4, and C/EBP-β. In addition, the interleukin (IL)-8 cytokine is also known to trigger the secretion of phosphorylated DEK under inflammatory conditions. Meanwhile, several pathways that trigger DEK overexpression in proliferative conditions include E2F, ERα, NF-Y, and YY1. However, a study on these various molecular pathways would be more fitted to help determine the etiology of CRC and therefore is outside the scope of this review (11).

Related to its role in bridging the inflammatory-tumorigenesis process, although DEK is a core protein expressed by cells into the cytoplasm and the cell nucleus strictly regulates its secretion, extracellular secretion of DEK also fulfills several roles affecting both inflammation and tumorigenesis. DEK is a chemoattractant attracting leukocytes to specific locations to trigger autoimmune reactions by reacting with anti-DEK antibodies. DEK secretions can also initiate chromatin re-formation and other activities that impair normal cell functions and trigger pathogenetic reactions to produce transformation, chemoresistance, inflammation, and tumor development of surrounding cells (24,42,43). The expression of DEK has also been found to affect various inflammatory signaling pathways, one of which is NF-κB, a factor that plays a role in chronic inflammation and tumorigenesis. The increase in DEK expression was noted to trigger changes in NF-κB transcription activity through colocalization with the transcription factor p65, which would further trigger activation of tumorigenesis-supporting genes, such as cellular inhibitors of apoptosis proteins 2 (c-IAP2), a part of inhibitors of apoptosis proteins (IAP) family, and IL-8 which is pro-metastatic (11,41).

The applicability of DEK as a prognostic biomarker for colorectal cancer. The expression of DEK can be detected by immunohistochemistry, using 3,3'-diaminobenzidine as the chromogen and hematoxylin as the counterstain (16). Therefore, the practicality of DEK as a prognostic biomarker varies according to whether the health facility has pathology installations able to conduct immunohistochemistry examinations. The evaluation approach is mainly semi-quantitative, using either positively stained cell count, referencing other

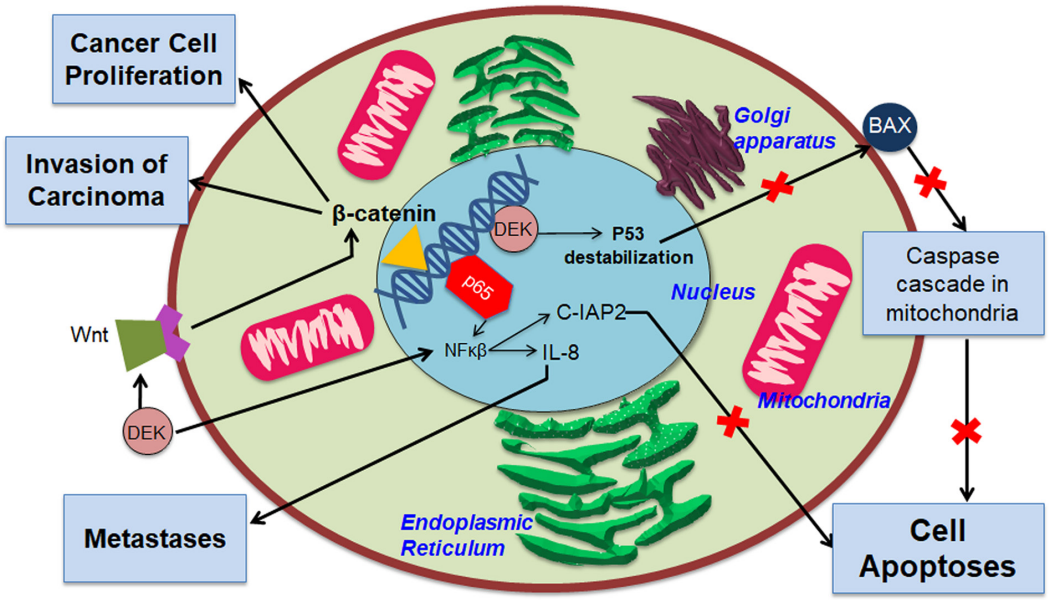

Figure 1. Schematic summary of the mechanisms and roles of DEK in tumorigenesis and pathogenesis of CRC. DEK can activate the Wnt/β-catenin pathway, inducing cancer cell proliferation and invasion. Colocalization of p65 with DEK activates NF-κB, causing the anti-apoptotic effect of c-IAP2 and pro-metastatic effect of IL-8. DEK also induces p53 (11,21,37-43). BAX, Bcl-2-associated X protein; c-IAP2, cellular inhibitors of apoptosis protein-2; IL-8, interleukin-8; NF-κB, nuclear factor κB; Wnt, wingless-related integration site.

literature such as the Human Protein Atlas for cut-off points, or the HistoScore approach that counts the number of cells based on staining intensity (16-18). Lin *et al* used a defined cut-off to define the positive expression of DEK if 5-25% of cells were stained and robust expression of DEK if >25% of cells were stained (16,21). Other methods used include ordinal scoring systems and positive or negative expression measures using western blot analysis instead of immunohistochemistry (19,20). A semi-quantitative cut-off measuring the area of stained cells in tissue samples might decrease the possibility of bias. Regarding accuracy, despite the studies reviewed, no actual clinical data have confirmed the accuracy of DEK in projecting CRC prognosis and comparing it to other options existing in current clinical settings. However, since many previous studies have reported the association between DEK and CRC prognosis, its potential as a prognostic biomarker for CRC should be pursued through further research.

Additionally, in the clinical setting, given that CRC is a complex disease with multiple carcinogenic pathways and several cases found to be associated with inflammation and autoimmune disorders, we suggest that testing of several biomarkers involved with DEK may be conducted only to distinguish the role of DEK in CRC etiology, whether it is dominated by inflammatory or tumorigenesis and proliferative process (11). The testing of molecules from other pathways may be more useful in the case of pre-cancer conditions, such as adenoma or polyps of the colon and rectum, to better understand the involved pathways of progression from these tumors to malignancy, whether it be chronic inflammation or proliferation that trigger DEK overexpression. However, in the clinical context of determining CRC prognosis, these tests need not be conducted because there is no further implication of these biomarkers on the overexpression of DEK and its impact on the (generally worse) prognosis of CRC.

In the setting of further research, however, conduction of testing for DEK overexpression along with other biomarkers related to it and CRC prognosis would be essential to validate and compare the prognostic accuracy of this biomarker compared with other, more established biomarkers, such as microsatellite instability (MSI) status (indicative of good prognosis), *KRAS*/neuroblastoma RAS viral oncogene (*NRAS*) mutation (poor prognosis), and v-raf murine sarcoma viral oncogene homolog B1 (*BRAF)* mutation (poor prognosis, primarily related to metastasis), for which comparative studies with DEK and each other are still unknown (44). This knowledge gap can be a great opportunity for researchers to better understand the role of DEK in CRC prognosis. Our review also indicates a dearth of literature regarding comparisons between DEK and other prognostic biomarkers of CRC or differences in prognosis between CRCs caused by different pathogenetic pathways. This is a significant knowledge gap that may provide for excellent research topics in the future.

Based on the present review, the authors found that DEK has promising potential as a biomarker for CRC prognosis for several reasons. First, DEK is expressed by cells from all human body tissues, but its overexpression is linked with cell proliferation conditions, especially in carcinogenesis (26,41). Therefore, overexpression of DEK is one of the potential biomarkers of carcinoma progression in various types of cancer, as the authors have stated at the outset, including in the colon and rectum. Second, the involvement of DEK in tumorigenesis and CRC pathogenesis is quite extensive, where DEK can affect tumorigenesis from various mechanisms. DEK is also involved in several inflammatory pathways; thus, it can be used as a biomarker in CRC cases, given that several CRC cases are associated with inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis (41,45). Third, as noted by Martinez-Useros *et al* (17,18), DEK can be a marker of

CRC tissue response to irinotecan-based and fluoropyrimidine-based CRC chemotherapy.

5. Conclusions

Summarizing the current literature, several pieces of evidence show that DEK is a promising prognostic biomarker of CRC. Overexpression of DEK is related to apoptosis avoidance, epithelial-mesenchymal transition, and more infiltrative cancer, and is clinically significantly associated with several clinical and pathological features of CRC, such as tumor size, lymphatic node metastasis, serous tissue invasion, and therapy response to specific chemotherapeutic regimens, generally predicting worse CRC. It was also proven to predict worse survival. The clear pathogenesis and clinical association between DEK and worse features of CRC makes it capable of being used as a biomarker to predict CRC prognosis in a clinical setting by histopathological analysis through immunohistochemistry, then quantitative and semiquantitative analysis of its expression. The role of DEK in the multiple pathogeneses of CRC and comparison to other prognostic biomarkers are prime subjects for further research.

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Authors' contributions

MH and MPW conceptualized the review and created the study methodology. MH, MPW, and SS curated the data, investigated the studies used in the review, and prepared the original draft of this review. MH created the visualization aids used in this review. MH and NR confirmed the validity of the raw data and findings cited in this review. NR supervised and validated the operation of this review and approved the final version of the manuscript. All authors reviewed and edited the draft and read and approved the final manuscript for publication.

Ethics approval and consent to participate

Not applicable; the article is a literature review.

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Competing interests

The authors do not have any conflicts of interest.

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