Cytokeratin 19 (CK19) as a marker for Epithelial Differentiation and Malignant Transformation: Its Clinical relevance in Diagnosis, Prognosis and Treatment response monitoring

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Abstract- ***Cytokeratin 19 (CK19) is a type I cytokeratin found mostly in epithelial tissues with high plasticity such as stem cells, transforming cells or tumorous cells. CK19 increases its expression level during epithelial embryogenesis, tissues regeneration, tissue repair as well as tissue development and has shown to have an increasing expression in carcinogenesis of CK19-positive cancers from normal tissues to premalignant lesions to carcinoma in situ. The insertion of CK19 in CK19-negative carcinoma cells induced the metastatic progression characterized by angiogenesis, invasion to surrounding tissues, increased proliferation and drug resistance. Hence, the detection of intracellular CK19 protein by immunohistochemistry (IHC), CK19 transcripts by quantitative Real time RT-PCR or One-step nucleic acid amplification (OSNA) and serum CK19 fragments such as Cyfra 21-1 by enzyme-linked immunosorbent assay (ELISA) could help in diagnosis to confirm the presence of the cancerous cells, in prognosis to predict the course the cancer is mostly likely to take and in treatment response monitoring to investigate the effectiveness of the treatment so that the early adjuvant therapy could be used in case the treatment was found ineffective during the follow-up studies***

Index Terms- ***Cytokeratin 19, epithelial differentiation, malignant transformation, diagnosis, prognosis, treatment response.***

I. INTRODUCTION

Cytokeratins (CKs) are filamentous proteins found throughout the cytoplasm of the epithelial cells. Their main function is to render elasticity to epithelial cells in order to support their structural integrity in present of the shearing force but also, they are involved in cellular processes such as intracellular transport, apoptosis, cell polarity and motility, cell growth and proliferation [1]. CKs are of two types: type I which is a group that belongs to acidic CKs numbered from 9 to 20 and type II which belongs to neutral and basic CKs numbered from 1 to 8. This review focuses on the involvement of the CK19 in cellular differentiation and transformation but also evaluates the relevance of CK19 in diagnosis and prognosis of various cancers of epithelial origin and the possibility of CK19-targeted treatment monitoring.

A. History of CK19

The word keratin which comes the Greek "kera" meaning horn, was first used in literature as far back as 1850 to designate the hard tissues found in the horns and hooves of animals [2]. Cytoplasmic keratin which came to be known as "Cytokeratins" were discovered for the first time by Steinert et al. in 1976 due to their spontaneous self-assembly properties observed in denatured cytokeratin filaments [3]. The name Cytokeratin 19 was introduced by Moll et al. in 1982 after mapping the cytokeratin profiles of squamous cell carcinoma lines. Among 19 cytokeratins mapped using 2D-SDS PAGE, the keratin with the lowest molecular

weight of 40 kDa and an isoelectric point of 5.3 was nominated Cytokeratin 19 [1].

B. CK19 molecular structure

Like all CKs, CK19 is made of 3 domains: a head, a central rod and a tail. Through sequencing analyses, human CK19 was found to have 400 amino acids (aa) in length including the initiating methionine with a non-helical N-terminal "head" domain of 79 aa (1-79), an alpha-helical central "rod" domain of 307 aa (80-387) and a short alpha-helical C-terminal tail domain of 13 aa (388-400) [4].

C. CK19 distribution in normal epithelia

Unlike other CKs which are restricted to particular location within epithelial tissues, CK19 occurs in both simple and stratified squamous epithelial tissues. CK19 is mostly found wherever different epithelial phenotypes coexist in close proximity or in different cell types of the same epithelial tissues such as mixed epithelia of the glands and the gland ducts or in diverse tissue phenotypes of the epithelia. In adult normal epithelia CK19 was found to be expressed in gallbladder, hepatic ducts and pancreatic ducts, endometrium, fallopian tube, breast, bladder, lungs, bile ducts, cervical glands, kidney collecting ducts, ovarian epithelium, salivary gland acini, thyroid epithelium [5].

D. Uniqueness of CK19

CK19 is the smallest of the known CKs and possesses an α-helical tail while other CKs have a non-helical tail. CK19 is the only type I CK without a specific partner. It usually partners with CK7 but it was found to be co-expressed also with CK8 when forming intermediate filaments. Unlike other CKs, under normal circumstance, which are restricted to specific tissue distribution, CK19 is not limited to either simple or stratified epithelia. Its expression is characteristic of the flexibility of progenitor cells which are not yet committed to any local differentiation. This state is labile and unstable and could be vulnerable to various transformation [6].

E. CK19 as a biomarker

The conservation of CKs during epithelial transformation and tumour development assist in understanding and classification of various carcinomas. CK19 is known to be a specific as well as a non-specific tumour marker of epithelial cancers. Most carcinomas are resultant of misregulation of CK19 expression either through its overexpression or its downregulation. In this context, the knowledge of CK19 implication in the epithelial differentiation, premalignant, malignant and metastatic transformation could be important to define how relevant CK19 may be as a diagnostic, prognostic and treatment monitoring marker.

II. CK19 AS A DIFFERENTIATION MARKER

The likelihood of CK19 being the neutral CK in differentiation epithelial cells is evidenced by the fact that CK19 is the first type I CK to be expressed in simple epithelia before their migration into suprabasal layer to continue their differentiation where the other type I CKs are synthesized, suggesting CK19 is involved in stabilization of early synthesized type II CKs thus delaying the expression of other type I CKs. This could explain why CK19 is abundant within epithelial tissues of the basal cell layer rather than differentiating suprabasal layer [6].

A. Placental development

In CK19 null transgenic mice, defects are apparent only when mice are exposed to a less-protected environment. This may be due to compensatory functions of CK18 which is co-expressed in the extra-embryonic tissues and CK20 which is co-expressed in the intestinal epithelia. Compound homozygous embryos lacking both CK8 and CK19 die in utero due to defects in the placenta, concluding that the proper development of the placental tissues requires the cooperation of both CK8 and CK19 [7].

B. Epithelial differentiation

CK19 mRNA is detectable in embryos of 6-8 days and its induction coincides with differentiation of cells giving rise to the trophectoderm, the extraembryonic endoderm and the embryonic ectoderm. In fetal human

skin, CK19 positive cells are found in basal layer whereas in adult human skin, they restricted to the outer root sheath of the hair follicle and not in the epidermis. These expressions are characteristic of pluripotent cells and stem cells which conclude CK19 to be a marker for epithelial progenitors [8]. The reduction in progenitor cells with the increase of age is apparent considering the wound healing of second degree burn patients faster in children compare adults [9].

C. Intestinal renewal

The similarity between the changes in intestinal CK19 expression during late embryonic development and those seen during crypt-to-villus differentiation in adult rat provide evidence for a specific role of CK19 in differentiating enterocytes. Starting at the period of maturation (18-19 days of gestation) characterized by formation of the intestinal villi, CK19 is found to be the major intermediate filament component of the intestinal epithelial cells. This increase of CK19 expression is also observed during crypt-to-villus differentiation [10].

D. Pancreatic differentiation

CK19 expression in the pancreas is associated with pancreatic differentiation. Upon induction of pancreatic differentiation in developing pancreatic epithelium and in pancreatic duct cells there is an increase in CK19 expression which start decreasing as the differentiation goes on. At the end of pancreatic differentiation almost no CK19 expression is found. This is confirmed within beta cells which do not express CK19 [11].

E. Sexual gonad differentiation

Expression of CK19 in gonads is sex-dependent. In the female fetal gonads, CK19 mRNAs are detected in ovaries up to two weeks after birth whereas in the male gonads, they are detected only after 13.5 days of gestation, suggesting the possibility of CK19 as a neutral CK during sexual differentiation since during testis differentiation, CK19 disappears simultaneously with the differentiation of Sertoli cells while in the ovary, no such shift has been observed [12].

III. CK19 AS A PREMALIGNANT TRANSFORMATION MARKER

Premalignant transformation refers to the process in which normal tissues pass through before becoming cancerous, hence the name precancerous disorders. Oral cavity is characterized by constant regeneration due frequent frictions and irritations which make the epithelia vulnerable to transformation. Oral potentially malignant disorder (OPMD) is a collective term used to designate both precancerous lesions and conditions of oral cavity with oral leukoplakia the most common followed by oral erythroplakia, and the least common are oral lichen planus and oral submucous fibrosis [13].

A. Oral Leukoplakia

Oral Leukoplakia (OL), also called smoker's keratosis, is a white patch caused by the mouth's reaction to chronic irritation of the mucous membranes. CK19 expression pattern increases significantly with the degree of epithelial transformation from NOM (normal oral mucosa) to OL (without dysplasia) to OLD (with dysplasia) to OSCC [14].

B. Oral Erythroplakia

Oral Erythroplakia (OE) is a red plaque found in oral mucosa. Its presence does not exactly mean cancer but it has a high risk of developing into cancer. The expression rate of CK19 in OE correlates with transformation of OE into dysplasia or carcinoma in situ or oral squamous cell carcinoma (OSCC). In normal oral mucosa, CK19 stains only basal cell layer while in dysplasia (mild-to-severe), it stained both the basal and supra-basal layer indicating that it may predict the possible premalignant transformation [15, 16].

C. Oral submucous fibrosis

Oral submucous fibrosis (OSF) is oral premalignant disorder which affect the submucosa tissues. CK19 is not a marker to be used in order to find and characterized the conversion of OSF into OSCC because CK19 expression profile does not show any

potential difference in staining different stages of OSF [17].

D. Oral lichen planus

Oral lichen planus (OLP), unlike OE, presented mild dysplastic alterations without exhibiting a trend for malignant transformation. CK19 expression in OLP does not present significant differences when compared to its expression pattern in mild dysplasia concluding that increase of CK19 expression pattern in OLP does not correlate with its malignant transformation [18].

OPMD such as OE and OL have higher malignant transformation rate ranging from 3 to 30% for OE and from 1 to 15% for OL compare to OLP and OSF which have around 1% transformation rate both. CK19 is found only to be a transformation marker of OE and OL and not of OSF nor OLP. This could be due to the fact that CK19 expression in OE and OL represented the ongoing transformation unlike in OSF and OLP where CK19 expression could be due to changes already made from normal tissues to OSF or OLP.

IV. CK19 AS A MALIGNANT TRANSFORMATION MARKER

A. Oral carcinogenesis

Oral cavity carcinogenesis process was studied for the first time using 4-nitroquinoline-l-oxide (4NQO) mouse model introduced in 1973 by Wallenius and Lekholm [19]. 4NQO is a chemical carcinogen which causes DNA damages similar to those caused by carcinogens found in cigarette smoke. This model was used to confirm CK19 involvement in oral cavity carcinogenesis. The intensity of CK19 expression increases from normal oral tissues to dysplasia (from mild to moderate to severe) with the highest expression observed in (OSCC). Thus, the increase of CK19 levels in oral epithelia is associated with malignant transformation [20].

B. Liver carcinogenesis

The carcinogenesis of the liver was studied within Resistant-Hepatocyte (R-H) model which is capable of identifying distinct lesions (preneoplastic foci, preneoplastic nodules, early and fully developed HCCs, and occasional features of combined hepato-cholangiocarcinomas) at well-defined timings and confirmed that CK19 expression rate increases with malignant transformation. CK19 positivity also confirmed that its expression is acquired along the way and does not reflect the cells of origin of tumor but their plasticity [21].

C. Cervical carcinogenesis

During cervical carcinogenesis, CK19 expression outspreads from the basal layer where stem cells live to the suprabasal layer, where transformed cells are expressed. CK19 stains the transformation zone wherein progenitor cells differentiate into squamous cell and columnar cell of the cervix and these are the same progenitor cells which transform into carcinoma in situ (CIN). Thus, CK19 is a transformation marker of cervical cancer when expressed in the suprabasal layer [22].

V. CK19 AS A METASTATIC TRANSFORMATION MARKER

Metastasis refers to the development of tumours in distant organs away from their primary location. These primary tumours acquire certain modifications which enable them to penetrate lymphatic or vascular circulation before reaching secondary organs [23]. Various studies have confirmed CK19 to be directly involved in metastatic transformation of primary tumours by promoting cancer cell survival, drug resistance, invasion, and angiogenesis. Most importantly, CK19 expression in these metastatic tumours is characterized by poor clinical outcome [24, 25].

A. Breast cancer metastasis

The expression of CK19 in a CK19-negative BT549 cell lines helped to understand the differences between CK19-positive cells and CK19-negative cells and the effect CK19 has on cells when they express it. It was found that the expression of CK19 in BT549 cells caused metastatic progression by arresting cell cycles, reducing cell motility and also increasing drug resistance. Hence, CK19 expression makes CK19-

negative cancer cells more metastatic compare with cancer cells that do not express CK19 [24].

B. Thyroid cancer aggressiveness

The correlation between the dedifferentiation rate and CK19 expression in thyroid cancer aggressiveness was confirmed using CK19 fragment, CYFRA 21-1 assay in dedifferentiated thyroid carcinoma (de-DTC), an advance carcinoma resistant to 131I and differentiated thyroid carcinoma (DTC) which is sensitive to 131I. CK19 overexpression in thyroid carcinomas is followed by extra thyroid invasion and higher TNM stage [26]. This is confirmed through serum Cyfra 21.1. Only de-DTCs showed CYFRA 21-1 positivity, not DTCs. These de-DTCs are aggressive and also shows high proliferation. Thus, CK19 overexpression in advanced thyroid carcinoma is associated with high aggressiveness.27

C. Hepatocellular carcinoma metastasis

The study of CK19 involvement in HCC tumor progression showed that CK19-knockdown in HepG2 does not influence the tumor growth whereas CK19-positive cells showed increased metastatic characters such as spreading to the neighboring cells and the connective tissue cells. The analysis of the ability of CK19-knockdown HepG2 cells for metastatic colonization after tail vein injection showed that CK19 knockdown significantly reduces HepG2 colonization into the lung and liver, suggesting CK19 negativity affects the ability of HCC cells to extravasate and colonize distal tissues [28].

VI. CK19 AS A DIAGNOSTIC MARKER

Early diagnosis of tumours followed by immediate treatment have shown to improve the prognosis of several cancer cases. For many years, the study of the morphology of the cells using conventional histopathology has helped to diagnose various cancers, but it usually produces false results and insufficient details about the cancer. However, the supplementation of molecular techniques such as IHC or ICC has improved both the sensitivity and specificity of the cancer diagnosis by relying on genetic variants associated with cancers and uses them as their surrogate markers.

CK19 is suggested to be an epithelial stem cell marker as it correlates with differentiation potential. Its level is highest in epithelial stem cells decreasing during differentiation and becomes absent in specialized cells. A reverse process is observed during carcinogenesis where there is an increase in CK19 levels as the dedifferentiation progress with poorly differentiated cancers showing highest CK19 expression. CK19 was proposed as a possible marker for epithelial tumours by Bjorklund in 1957 who found it reproducible and highly sensitive as a broad epithelial marker for carcinoma detection [29].

IHC is a method first implemented by Albert Coons in 1941 which uses light microscope to detect cellular components in a tissue by exploiting the antibody-antigen binding specificity and color-producing reaction between enzymes and substrates [30]. CK19 detection by IHC in various epithelial cancer has shown CK19 to be a successful diagnostic marker (Table I).

PCR involves the conversion of the target mRNA to cDNA, followed by its amplification from single to thousands to millions of copies. Traweek and coworkers in 1993 described PCR to be highly sensitive in the detection of CK19 gene transcripts [31]. The introduction of quantitative reverse transcriptase-PCR (qRT-PCR) improved the sensitivity and specificity of tumour detection but most importantly was the quantification it offers which helps in staging of cancers (Table I).

TABLE I - SUMMARY OF STUDIES OF CK19 AS A DIAGNOSTIC MARKER

Type of Cancer	Study	Notable Outcomes	Reference
Endometrioid adenocarcinomas (EAC)	IHC	Even though normal endometrium had CK19 expression, the strong expression was seen in EAC and in myometrial invasions.	Stewart et al. [32]
Yolk sac tumours (YST)	IHC	CK19 expression distinguished YST and also confirmed YST metastases in the lung, lymph nodes, and ovaries.	Bremmer et al. [33]
BCC and Sebaceous	IHC	CK19 had a strong immunoreactivity in BCC but stained focal areas of cyst or duct formation in sebaceous tumors.	Hyel and Mehregan [34]
Papillary thyroid carcinoma (PTC)	IHC	The cut-off threshold above 10% for CK19 resulted in a sensitivity and specificity of 93% and 100% respectively.	Khurana et al. [35]
Lung cancer	IHC	Positive cytoplasmic staining of CK 19 in NSCLC correlated well with the increasing tumour grades	Nasseem et al. [36]
	RT-PCR (peripheral blood)	Expression of CK19 mRNA was associated with the pathology of NSCLC and micrometastasis.	Zhang and He [37]
Breast cancer	RT-PCR (peripheral blood)	High CK19 levels predicted independently non-sentinel lymph node (nSLN) status before surgery	Yu et al. [38]
Gastric cancer	RT-PCR (lymph nodes)	CK19 mRNA detection is sensitive and specific and it is superior to routine histopathology.	Suo et al. [39]
Pancreatic adenocarcinoma	IHC	CK19 expression confirmed the diagnosis of pancreatic adenocarcinoma	Zapata et al. [40]
Head and neck cancer (HNC)	RT-PCR (lymph nodes)	CK19 detection in lymph nodes of HNC patients confirmed the existence of micrometastases	Tao et al. [41]

VII. CK19 AS A PROGNOSTIC MARKER

Prognosis represents the predictive course of the disease. The most used prognostic factors include tumour size, lymph node presence and metastasis. CK19 as a prognostic marker can be confirmed during diagnosis in respect of the tumour size. The increase in size of the epithelial tumours correlate with poor prognosis and usually with increased dedifferentiation rate which in return correlate with CK19 expression.

Metastasis is the migration of cancerous cells from the primary tumors into distant organs via bloodstream or lymph systems. These migrating cells are known as circulating tumor cells (CTCs). When CTCs disseminate into secondary organs, they are termed disseminated tumor cells (DTCs). The detection of DTCs in bone marrow, cerebrospinal fluid, as well as lymph nodes is of great importance because they are responsible tumor metastasis, thus poor prognosis.

The detection of the transcripts from CTCs using epithelial markers specific only to CTCs with RT-PCR was found capable of detecting one CTC in 106 normal appearing cells. Due to the clearance of RNA in blood by RNAses, their presence in high levels confirm the existence of highly proliferating cells. The RT-PCR has shown to be more sensitive than IHC but it was suggested that these two techniques can complement each other with RT-PCR used for its high sensitivity and IHC to examine the morphology of detected cells, thereby differentiating contaminating cells from metastatic cells [42].

The metastatic cancers are found to be highly proliferative resulting in a release of CK19 fragment, CYFRA 21-1. CYFRA 21-1 levels are inversely proportional with intratumoral CK19 expression, which means high CYFRA 21-1 levels means CK19 absence intratumorally and vice versa. The detection of CYFRA 21-1 was done for the first time in lung cancer using ELISA by Stieber et al. in 1993 [43]. CYFRA 21-1 detection in various epithelial cancers confirmed its correlated with poor prognosis (Table II).

TABLE II - SUMMARY OF STUDIES OF CK19 AS A PROGNOSTIC MARKER

Type of Cancer	Study	Notable Outcomes	Reference
Colorectal cancer (CRC)	RT-PCR (blood)	High preoperative CK19 mRNA levels correlated with poor survival, while low preoperative levels were with good survival	Xu et al. [44]
Breast cancer	Flow cytometry	CK19 expression correlation with tumor size and tumor progression and poor prognosis	Brotherick et al. [45]
	ELISA	High levels of CYFRA21-1 correlated with tumor size and clinical stage of the disease	Ebieda et al. [46]
Gastric cardia cancer (GCC)	RT-PCR (blood)	Elevation of preoperative and postoperative CK19 mRNA levels correlated with poorer prognosis	Qiao et al. [47]
Oral squamous cell carcinoma (OSCC)	IHC and RT-PCR	CK19 was associated with higher tumor recurrence rate and lower survival rate	Zhong et al. [48]
Pancreatic endocrine tumors (PETs)		CK19-positive tumours classified as 1b and 2 by WHO behaved more aggressively than their CK19-negative tumours.	Schmitt et al. [49]
Tongue cancer	IHC	CK19 positivity in SCC of the tongue was associated with a reduced overall survival (OS)	Ernst et al. [50]
Gastrointestinal Cancer	RT-PCR	Positive expression of CK19 mRNA in advanced gastrointestinal cancer correlates with poor prognosis	Du et al. [51]
Hepatocellular tumours	IHC	CK19 marks poor differentiation and a more aggressive behaviour of HCC and predicts tumour recurrence	Van Sprundel et al. [52]
Hepatoblastoma (HB)	IHC	CK19 expression correlated with aggressive behaviour in HB and poor prognosis	Kiruthiga et al. [53]
Head and neck cancer (HNC)	RT-PCR	CTCs are detected in advanced stages of HNSSC and correlate with poorer prognosis	Winter et al. [54]
Ovarian cancer	IHC	High frequency of Ovarian CSCs in epithelial ovarian tumors correlated with short progression-free intervals.	Liu et al. [55]

VIII. CK19 AS A THERAPEUTIC MARKER

Ineffectiveness of cancer treatments such as radiotherapy, surgical resection, hormonotherapy or chemotherapy is usually due to the presence of CTCs and DTCs which are missed by conventional diagnostic tests causing the recurrence and relapses. Their early detection could improve the treatments of various cancers as contrary to the follow-up studies which take a long time. The use of treatment response monitoring markers could show as early as possible the ineffectiveness of the drug which could help to start adjuvant therapy earlier and improve the treatment response.

The detection of DTCs before the treatment has been introduced recently and has been successful in detecting the presence of micrometastases in lymph nodes. OSNA (one-step nucleic acid amplification) is a CK19 mRNA-based intraoperative diagnostic assay that detect solitary lymph nodes (SLN) [56]. It was found to the most sensitive assay to detect micrometastases compare to qRT-PCR and IHC. OSNA is currently being used to detect SLN in breast cancer and has been used successfully to detect SLNs in various cancers (Table III).

TABLE III - SUMMARY OF STUDIES OF CK19 AS A TREATMENT MONITORING MARKER

Type of Cancer	Study	Notable Outcomes	Reference
Non-small cell lung cancer (NSCLC)	RT-PCR	Positive CK19 mRNA expression in PB after definitive chemo-radiation was an unfavorable prognostic predictor	Chen et al. [57]
Head and neck cancer (HNC)	ELISA	CYFRA 21-1 levels dropped significantly 24 hours after successful operation.	Kwarciak et al. [58]
Endometrial cancer (EC)	OSNA	OSNA represent an efficient intra-operative tool for early-stage EC detection	Fanfani et al. [59]
Lung cancer	ELISA	Serial monitoring of CYFRA 21-1 could be a useful prognostic tool of treatment response and longer survival	Hamzaoui et al. [60]
	RT-PCR	CTCs could be valuable for evaluating the efficacy of radiotherapy and deciding on systemic therapy.	Ge et al. [61]
	OSNA	CK19 mRNA was the best biomarker for lymph node metastases detection in NSCLC	Inoue et al. [62]
Breast cancer	Flow cytometry (blood)	Though not sensitive as RT-PCR but offered the possibility to monitor disease progression and the risk of relapse	Wang et al. [63]
	ELISA	Elevated preoperative levels of serum CYFRA 21-1 decreased to normal levels after curative operation	Nakata et al. [64]
	OSNA	OSNA is a reliable tool for intraoperative diagnosis of whole SLNs during surgery of breast cancer.	Chaudhry et al. [65]
Human hepatocellular carcinoma (HCC)	ELISA	CYFRA 21- 1 levels were regulated by CK19 function and reflected the treatment efficacy in CK19-positive HCC-CSCs.	Kawai et al. [66]
	IHC (lymph nodes)	CK19 expression in regional LN of HCC was associated with LNM and an extremely poor outcome after operation	Lee et al. [67]
Colon cancer	OSNA	OSNA had high sensitivity and specificity in detecting small lymph node tumor infiltrates	Güller et al. [68]

The easy access to blood which is the source of CTCs could assist the monitoring of the treatment during follow-up studies. Periodic collection of blood during treatment and their assessment for the presence of CTCs could assist in assessing the efficacy of therapy and foresee cancer relapse or recurrence cause by drug resistance. Another technique is to detect the expression levels of CYFRA 21-1 which correlates with the number and the proliferation rate of metastatic cells being treated (Table III).

IX. CONCLUSION

CK19 is unique in that its expression is either from epithelial stem cells with differentiation potential or in epithelial cells undergoing premalignant or malignant or metastatic transformation. CK19 presence marks the zone of transformation. Its expression in basal cells indicate the state of differentiation but in the suprabasal layer, it is usually associate with epithelial transformation. This could help diagnose various epithelial cancers in their early stages when their treatments could have better responses. However, more studies are still required to understand how it is involved in epithelial carcinogenesis. The increased levels of CK19 in primary tumours are mostly found to cause metastatic transformation and high aggressiveness compare to epithelial cancers which do not express CK19. Likewise, the increased levels of CK19 in metastatic tumours is correlated with poor prognosis and low survival rate. But, as it was seen, total absence of CK19 expression through gene silencing resulted in similar metastatic behaviors such as aggressiveness and poor prognosis, which highlight the importance of CK19 expression for the normal cell function. Its importance in cancer treatment monitoring is resultant of its involvement in metastatic progression of malignant tumors and its correlation with high proliferation within metastatic cells as evidence in the release of CYFRA 21-1. Its monitoring ability could be targeted for adjuvant treatment as these treatment-resistant cells express CK19 and their reduction could decrease their involvement in cancer recurrences and relapses. Further studies are needed to understand how effective this CK19-targeted treatment could be as an adjuvant targeted therapy. Thus, CK19 investigations could help improve the understanding of the carcinogenesis of various epithelial cancers, their diagnosis, prognosis as well as treatments.

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