Chromatin Remodeling and Transcription in Appendiceal Cancers

Subjects: Oncology

Contributor: Luisa Ladel , Wan Ying Tan , Thanushiya Jeyakanthan , Bethsebie Sailo , Anup Sharma , Nita Ahuja

Appendiceal cancers (AC) are a rare and heterogeneous group of malignancies. Historically, appendiceal neoplasms have been grouped with colorectal cancers (CRC), and treatment strategies have been modeled after CRC management guidelines due to their structural similarities and anatomical proximity.

appendiceal cancer chromatin epigenetics cancer biomarkers personalized oncology

1. Introduction

Although appendiceal cancers (AC) are rare, there has been a trend of increasing incidence of appendiceal malignancies since 2000, based on the National Cancer Database (NCDB). A 54% increase in appendiceal neoplasms in the USA over the past 10-year period has been noted, with a reported approximate incidence of 0.12 to 2.6 cases per million people per year, in line with incidence reports from other North American and European countries [1][2][3][4][5][6]. Unfortunately, no incidence report is available for 2022, and no data regarding estimated global incidence exists. Epidemiological studies on appendiceal neoplasms from European and North American countries do not show any significant sex-based difference in incidence for most appendiceal cancer subtypes, except for appendiceal adenocarcinomas, which are more common in men, and neuroendocrine tumors, which are slightly more common in females [7][8]. Neuroendocrine appendiceal tumors have been observed to occur more frequently under the age of 50 years, while other appendiceal cancer subtypes appear more frequently with older age [1][2][9][10][11][12]. The 5-year survival rates for neuroendocrine and low-grade neoplasms of the appendix vary around 67–97%. Meanwhile, lower survival rates have been reported for more advanced and malignant histological subtypes, although specific statistics are not available due to the rare nature of these tumors [8].

Appendiceal cancers are commonly diagnosed intraoperatively during appendectomies [6][13]. Recent years have seen a shift toward nonoperative management of acute appendicitis [14][15][16]. This paradigm shift may contribute to missed or late diagnosis of appendiceal cancers. Hence, efforts to stratify and identify high-risk individuals and early-stage appendiceal cancers are crucial.

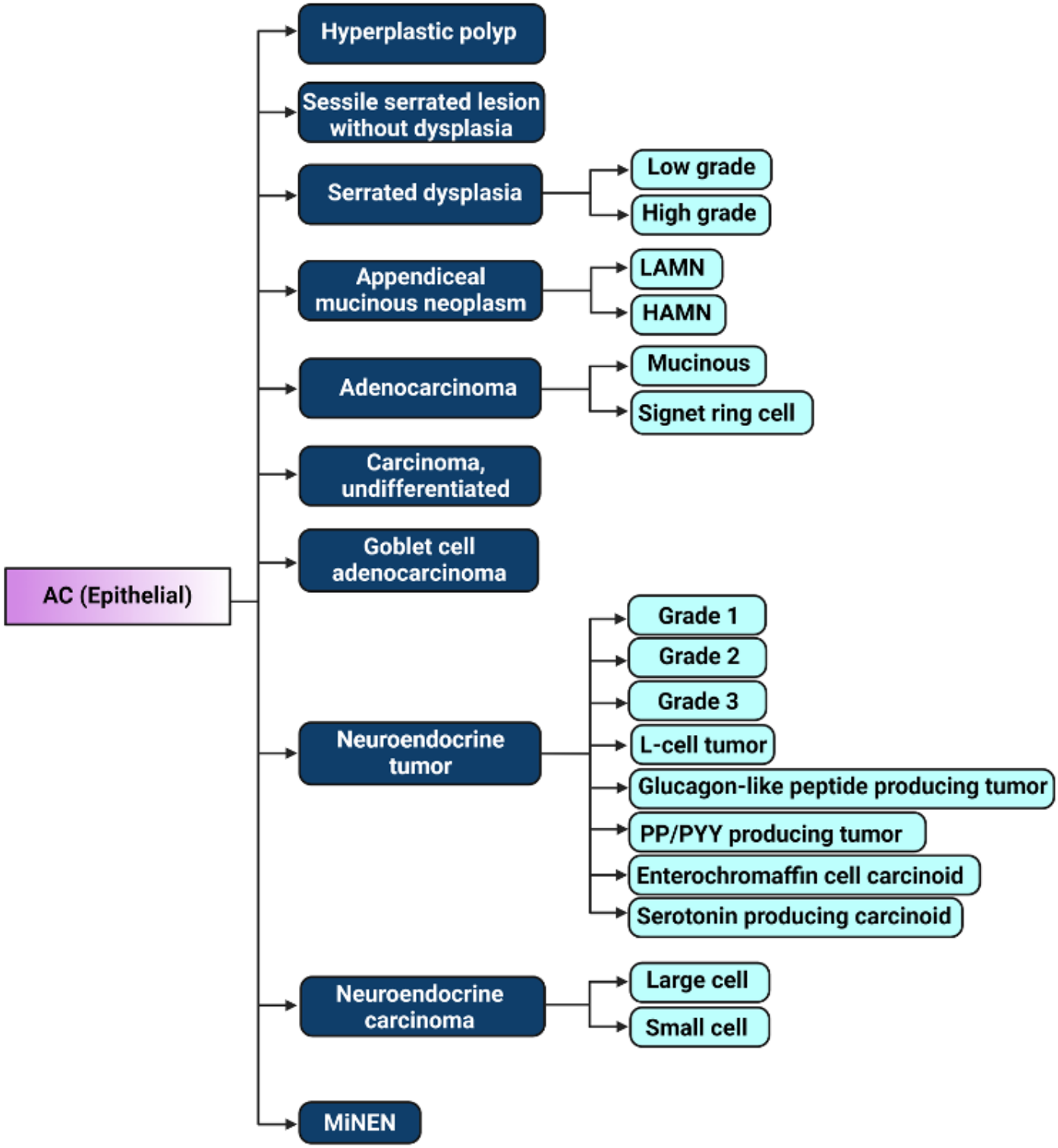

Figure 1. Illustration of 2019 WHO classification of epithelial appendiceal cancers [23]. LAMN: low-grade appendiceal mucinous neoplasm, HAMN: high-grade appendiceal mucinous neoplasm, PP/PYY: pancreatic polypeptide/peptide YY, MiNEN: Mixed neuroendocrine – non-neuroendocrine neoplasm. *Figure created with biorender.com.*

2. Chromatin Remodeling and Transcription in Appendiceal Cancers

Epigenetics modifications play an important role in chromatin modulation and are subject to environmental forces typically through its dynamic and reversible nature. However, they can also be heritable and persist over several generations [17]. The major epigenetic mechanisms include methylation, leading to the suppression or silencing of gene activation, and acetylation, causing the activation of transcription, both of which can take place on histones, affecting large areas of the genome, or in a more specific manner on DNA itself at the CpG sites of the promoter regions of specific genes. The other main categories of epigenetic mechanisms include chromatin remodeling by nucleosome positioning and regulation via non-coding RNAs [18]. Epigenetic changes in malignancy have attracted much attention, especially in gastrointestinal neoplasms, since they often occur early in carcinogenesis and involve key cancer-associated pathways [19][20]. Burgeoning evidence has shown that epigenetic signatures constitute crucial hallmarks of disease pathogenesis. This field has become an area of intensive research for biomarker development and novel therapeutic strategies in the era of precision medicine [20]. To our knowledge, appendiceal cancers have no established epigenetic alterations or signatures. However, mutational genomic data and pathway enrichment analysis from several molecular studies of appendiceal cancers has revealed genes and pathways that could potentially be involved in epigenetic regulation. The exploration of these genes and their regulatory pathways could provide deeper insights into the epigenetic landscape of appendiceal cancers.

2.1. SWI/SNF Chromatin Remodeling Complex

One of the essential epigenetic modulators is SWItch/Sucrose Non-Fermentable (SWI/SNF), one of four major families of chromatin-remodeling complexes and a key regulator of nucleosome positioning and modifier of gene enhancer accessibility. SWI/SNF has been shown to mediate cell differentiation and was also discovered to play a role in DNA damage repair by modifying chromatin structures around the site of DNA damage and recruiting proteins belonging to the DNA damage repair machinery [21][22]. The SWI/SNF complex consists of multiple subunits, several of which have been indicated to possess oncogenic potential [21][23]. Two subunits, ATPase SMARCA4 and complex-associated factor ARID1A, have been reported to be involved in DNA damage repair by assisting in homologous recombination-mediated DNA repair and non-homologous end joining at sites of double-strand breakage [24][25]. Both *SMARCA4* and *ARID1A* are mutated in appendiceal goblet cell carcinoids, mixed goblet cell carcinoid–adenocarcinomas, and some appendiceal mucinous adenocarcinomas and adenocarcinomas [26][27]. These mutations, and most other mutations affecting genes encoding for the SWI/SNF complex, lead to a loss of function of the respective proteins and have been linked to tumor progression in several malignancies, marking these genes as tumor suppressors [21].

2.2. COMPASS Chromatin Remodeling Complex

Another significant chromatin-remodeling complex is Complex Proteins Associated with Set1 (COMPASS). One of its main catalytically active components is the lysine-specific demethylase 6A histone demethylase KDM6A (or UTX) [28][29]. The type 2 lysine methyltransferases C and D (KMT2C and KMT2D) are enzymatically active by

methylating the histone 3 lysine 4 (H3K4me3). Their involvement in the regulation of gene expression is widespread. Mutations in *KMT2C*, *KDMT2D*, and *KDM6A* have been linked to the development of congenital disorders, emphasizing their importance for mammalian cell function through all stages of development and across various tissue types [30]. KMT2D has been studied extensively in prostate cancer and has also been shown to activate the PI3K/AKT pathway and support epithelial–mesenchymal transition pathways in carcinogenesis [31]. *KDM6A* and *KMT2D* mutations have been reported in the appendiceal goblet cell carcinoid, mixed goblet cell carcinoid–adenocarcinoma, and some appendiceal mucinous adenocarcinomas and adenocarcinomas [26][27].

Interestingly, the effects of *KDM6A* mutation are not uniform across different cancers and likely depend on the transcription factors it interacts with in each specific tissue type. For example, KDM6A has been implicated as a tumor suppressor in gastrointestinal malignancies. However, it appears to influence oncogenic transcription factors' activity in hormonally driven cancers. *KDM6A* has also been linked to EZH2; loss-of-function mutations in *KDM6A* seem to affect transcriptional repression by EZH2 and have been shown to increase susceptibility to treatment with EZH2 inhibitors [29][32].

2.3. The Forkhead Box O (FoxO) Transcription Factors

The Forkhead box O (FoxO) family of transcription factors regulates the expression of genes in crucial cell physiological events, including apoptosis, cell cycle control, glucose metabolism, and oxidative stress resistance. A central regulatory mechanism of FoxO proteins is phosphorylation by AKT downstream of PI3K, which leads to the disruption of FoxO DNA binding [33][34][35][36]. In addition, an association has been found between FoxO3 and the COMPASS-associated methyltransferase KMT2D, as loss of KMT2D function was found to cause enhanced vulnerability to DNA damage through the suppression of antioxidative gene transcription caused by diminished DNA binding of FoxO3, likely in a PI3K/AKT-independent manner [31]. FoxO signaling is enriched in appendiceal goblet cell adenocarcinoma compared to colorectal adenocarcinoma [37].

Epigenetics-based Biomarkers and therapeutic targets

A tremendous breakthrough in medical oncology was achieved with the introduction of immune checkpoint inhibitors. Exciting data proposes potential for treatment synergism between immunotherapy and epigenetic drugs, such as DNA demethylating agents. It has been shown that treatment with this class of drugs creates an Interferon-mediated immune response within the tumor microenvironment of hematological, ovarian, and colorectal cancers [38][39][40]. This is thought to enhance the efficiency of the antitumoral immune response, which has been hypothesized to increase even further in combination with immune checkpoint blockers. Furthermore, dysregulation of epigenetic silencing by DNMT1 inhibition via PI3K/AKT hyperactivation and aberrant activation of the TGFβ signaling pathway have been unmasked as key drivers behind immune evasion and lack of response to immunotherapy [41]. Other studies have revealed enhanced sensitivity to immune checkpoint blockade in tumors carrying SWI/SNF complex mutations. *ARID1A* deficiency led to significantly reduced tumor burden and prolonged survival upon immunotherapy compared to wild-type tumors in studies for ovarian and gastric cancers [21]. Likewise, deviant transcriptional regulation due to inhibition of EZH2 has been implicated in correlating with the

immunogenicity of tumor cells and immune silencing in the tumor microenvironment. The utility of combination therapies with EZH2 inhibitors and immune checkpoint blockers remains to be investigated further, with several clinical trials underway [42].

Exciting advances have also been made in recent years in EZH2-targeted therapies. EZH2 is mutated in specific forms of appendiceal cancers, and several of the other epigenetic regulators found to be mutated in appendiceal neoplasms have been linked in some form to EZH2 overexpression or hyperactivation as well; most prominently, PI3K/AKT, as well as KDM6A and specific subunits of the SWI/SNF complex. This makes EZH2 a prime therapeutic target, and several compounds have been developed since EZH2 inhibitor Tazemetostat was FDA approved for advanced epitheloid sarcoma as well as relapsed or refractory follicular lymphoma, with several ongoing phase 1 and 2 clinical trials investigating similar drugs, such as SHR2554 and CPI-1205 (or lirametostat) in small intestine neuroendocrine tumors and relapsed or refractory B-cell/T-cell and Hodgkin's lymphomas, respectively [43][44][45]. Another study linked EZH2-mediated epigenetic changes to chromatin density to increased resistance to DNA damage in cells with concurrent p53 mutation and presented data suggesting that resistance to treatment approaches with chemotherapy and radiation as conferred by p53 mutation could be overcome, at least in part, by EZH2 inhibition [42]. However, more than direct targeting of these mutations or their affected pathways are attainable treatment approach. There are, for example, encouraging data proposing the utility of existing DNA damage repair inhibitors in tumors with *KMT2D* mutations. These findings align with the increased susceptibility to DNA damage found in KMT2D-deficient tumors, as evidenced by increased sensitivity to PARP inhibitors [31]. Similar findings were obtained in tumors with mutations affecting the SWI/SNF complex. Specifically, PARP inhibitors are under investigation in several trials for tumors with *ARID1A* mutation, based on the involvement of the SWI/SNF complex in DNA damage repair and therapeutic vulnerability observed in preclinical studies [21].

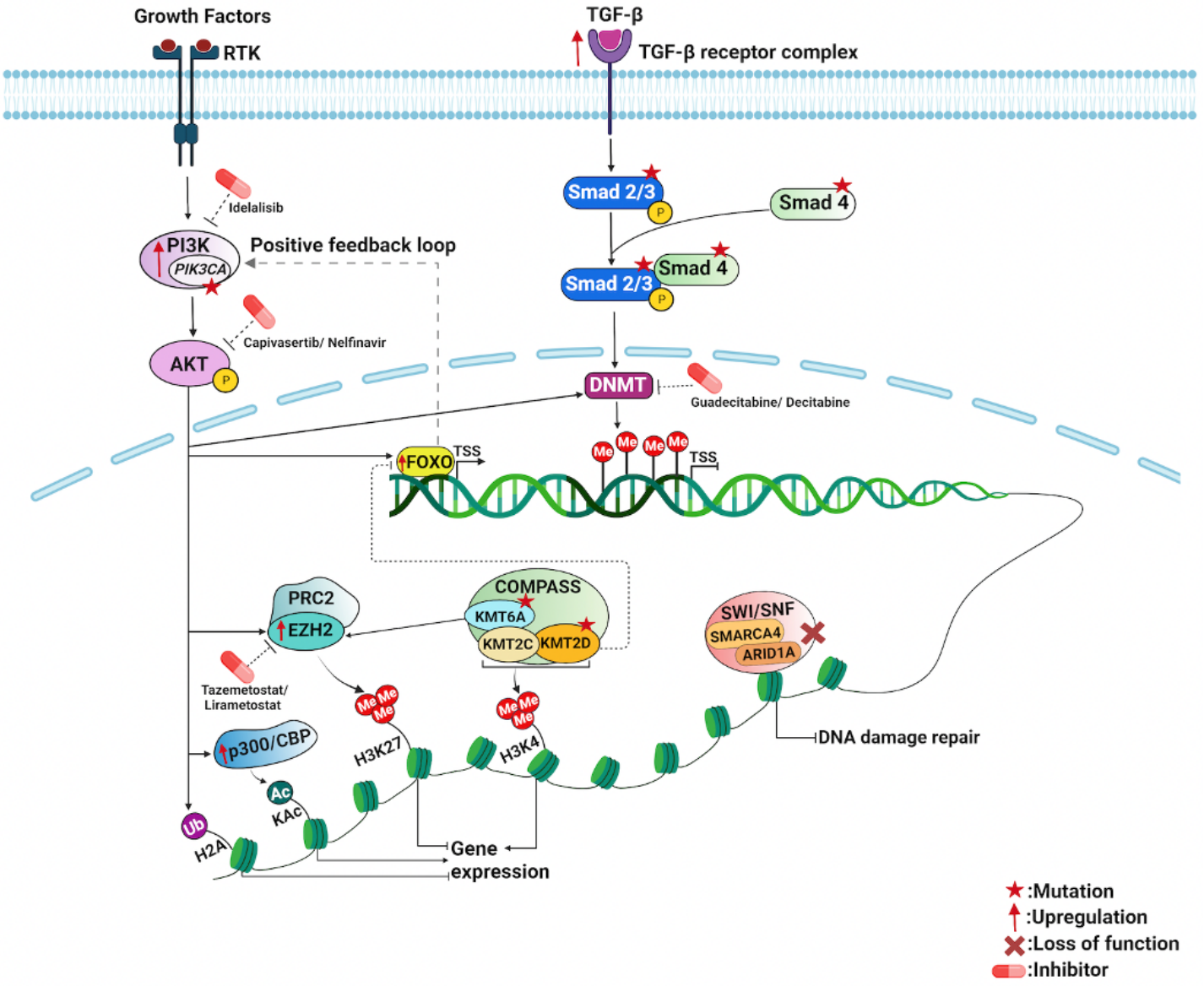

Figure 2. Major epigenetic pathways contributing to oncogenesis in appendiceal cancers and potential therapy-related targets. Ac: Acetylation, DNMT: DNA Methyltransferase, KAc: Lysine acetylation, Me: Methylation, P: Phosphorylation, RTK: Receptor Tyrosine Kinase, TSS: Transcription start site, Ub: Ubiquitination. *Figure created with biorender.com*

Epigenetic regulators present promising opportunities for developing biomarkers and translating treatment strategies from other malignancies into appendiceal cancers. Whole genome analysis of changes in methylation patterns may yield a wealth of information for clinicians dealing with appendiceal cancers, primarily as part of an individualized oncology approach, and even more so if utilized in liquid biopsy format.

3. Conclusions

The intricacies of epigenetic alterations and mechanisms in appendiceal neoplasms are still largely unknown. However, several epigenetic mechanisms have been postulated based on currently available data, which hold highly promising potential for clinical applicability regarding novel diagnostics and prognostication in appendiceal cancers. Further studies are necessary to validate previous findings in a methodical, epigenomics-centered, and translational approach. Epigenetics-based biomarkers may be the key to a deeper understanding of epithelial appendiceal cancer pathophysiology and aid in uncovering actionable targets for disease monitoring in appendiceal cancers. Ultimately this could enable clinicians to prognosticate responses to various therapy approaches, estimate the risk of progression or relapse and predict overall survival in their patients, thereby making personalized oncology a reality in managing and treating appendiceal neoplasms.

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