Mucins are high molecular-weight epithelial glycoproteins and are implicated in many physiological processes, including epithelial cell protection, signaling transduction, and tissue homeostasis. Abnormality of mucus expression and structure contributes to biological properties related to human cancer progression. Tumor growth sites induce inhospitable conditions. Many kinds of research suggest that mucins provide a microenvironment to avoid hypoxia, acidic, and other biological conditions that promote cancer progression. Given that the mucin layer captures growth factors or cytokines, we propose that mucin helps to ameliorate inhospitable conditions in tumor-growing sites. Additionally, the composition and structure of mucins enable them to mimic the surface of normal epithelial cells, allowing tumor cells to escape from immune surveillance. Indeed, human cancers such as mucinous carcinoma, show a higher incidence of invasion to adjacent organs and lymph node metastasis than do non-mucinous carcinoma. In this mini-review, we discuss how mucin provides a tumor-friendly environment and contributes to increased cancer malignancy in mucinous carcinoma. [BMB Reports 2021; 54(7): 344-355]

INTRODUCTION

The mucosal surfaces of the body protect against various external environments. The intestinal tract is the guardian of the innate host defense because of the secretory factors of intestinal goblet cells (1). Colonization by intestinal bacteria is limited to an outer mucus layer and interacts with mucin glycoproteins, whereas an inner mucus layer is entirely devoid of bacteria (2). Thus, the defection of mucus layers increases bacterial interaction with the surface epithelium. Additionally, abnormality of mucins and mucin structure has occurred in mucinous colorectal carcinoma (MCC) (3). Since tumor growth sites induce inhospitable conditions for them to survive, mucins are suggested as an oncogenic microenvironment that avoids hypoxia, acidic, and other biological hurdles. The composition and structure of mucins enable them to mimic the surface of tumor cells like the surface of normal epithelial cells (4). Additionally, the mucus layer captures growth factors or cytokines, contributing to cell growth of the tumor. Alternatively, these properties interfere with the interaction between the immune system and tumor cells. Indeed, a high concentration of soluble mucins downregulates the motility and activation status of leukocytes (5). It was also reported that cell surface mucin contributes to cell proliferation and differentiation (6).

MCC shows a higher incidence of invasion to adjacent organs and lymph node metastasis than does non-mucinous colorectal carcinoma (7). Also, MCC is characterized by a large amount of extracellular mucin, and mucin pools contain malignant epithelium (4, 7). However, the function of mucin especially in MCC pathology is not completely understood. Thus, the unveiling of mucin’s role and molecular mechanisms for MCC tumorigenesis and understanding MCC mouse models is required for MCC study. In this mini-review, we briefly discuss major MCC-related mucins and their roles in MCC development. Further, we introduce the currently known MCC therapeutic drugs and mouse models proposed for MCC study.

GEL-FORMING AND TRANSMEMBRANE MUCINS

The major constituent of mucus layers is mucins which are high-molecular-weight epithelial O-glycosylated glycoprotein (8) and are implicated in pathogenesis in cancer, especially mucinous adenocarcinomas. Currently, 21 mucin genes are known in humans. The mucins are classified into two groups based on their structure and functions: (i) secreted gel-forming mucins and (ii) transmembrane mucins. Gel-forming mucins including MUC2, MUC5AC, MUC5B, MUC6, and MUC19, cover epithelial cells in various organs (Table 1). Gel-forming mucins are secreted oligomeric mucin and might be responsible for the properties of mucin. Transmembrane mucins such as MUC1, MUC3, MUC4, MUC12, MUC13, MUC15, MUC16, MUC17, MUC21, and MUC22, exhibit monomeric structural characteristics and mainly located on the cell surface, and
The results of MUC2 deficient mouse developments colitis (11), methylation of the colorectal cancer (CRC) development, which is caused by Decreased MUC2 is highly involved in the early stage of component of the mucus layer in the small and large intestines. MUCIN2 (MUC2): Gel-forming mucins in cancer the survival of tumor cells (Fig. 1). Thus, it may lead to various physiological effects by increasing the chance of binding with a growth factor and cytokine for filling the space and raises its gel-forming character. Subsequent-ly, the promoter might contribute to CRC initiation. However, the results of MUC2 gene promoter methylation analysis of MCC and non-MCC by narrowing the scope in the entire CRC analysis shows demethylation in the MUC2 promoter of MCC (10). MCC (10-15% of human CRC) is metastatic and therapeutically resistant (12) and shows accumulated genetic mutations (10). MCC (10-15% of human CRC) is metastatic and therapeutically resistant (12) and shows accumulated genetic mutations including K-Ras, TOP-1, MAPK, and BRAF (12-18). However, MCC shows a low frequency of TP53 mutation and protein expression. Also, TP53 and p21 positively control MUC2 via transcriptional activation (19). These studies imply that MCC may show a genetic background difference from CRC for amplifying MUC2, at least for TP53 mutation or expression. Indeed, the Adenomatous polyposis coli (APC) mutation, with the highest frequency in CRC, is relatively low in MCC. In summary, CRC (non-MCC) downregulates MUC2 to foster an oncogenic environment by inflammation or colitis, whereas MCC might try to employ its unique genetic background for generating the mucinous environment including MUC2 secretion. MUCIN5AC (MUC5AC): In normal physiological conditions, MUC5AC is barely secreted in intestinal mucus (20). But, similar to MUC2, MUC5AC is expressed at a high level in MCC and by microsatellite instability (MSI)-high tumors (21, 22). Cancer patient tissues show MUC5AC-positive tumor cells (35-100%), which depend on the tumor type [Adenocarcinoma: 147/420 [35%], Adenocarcinoma 1-49% mucinous component: 119/167 [71%], Mucinous > 50%: 46/49 [94%]. Signet-ring cell carcinoma: 8/8 [100%] (23). Signet-ring cells produce aberrant mucin and demonstrate high levels of MSI. The mechanism of MSI generation is involved in the dysfunction of the DNA mismatch repair protein. In normal tissue, DNA mismatch repair proteins correct errors during DNA replication. However, impaired DNA mismatch repair proteins in tumor cells trigger the possibility of MSI generation, subsequently resulting in chromosomal instability (CIN). Hypomethylation of the MUC5AC promoter is a predictor of MSI (24). Furthermore, elevated MUC5AC is associated with mismatch repair-deficiency (25) and downregulation of TP53 and its target gene p21 (26), which are strongly related to the maintenance of chromosomal stability. Since β-catenin has been reported to induce impaired DNA damage repair via LIG4 (27), MUC5AC-induced β-catenin (26) might be involved in MSI via radioresistance. Although Wnt/β-catenin signaling contributes to radioresistance, MSI does not happen under Wnt/β-catenin signaling hyperactivated conditions that do not show an increase in mucins (28-30). Moreover, MUC5AC shows a negative correlation with MLH1, a protein for DNA damage repair, in MCC (22). Thus, it is likely that MUC5AC is a key cooperator for MSI, but veiled a detailed molecular mechanism. Recently, it was reported that MUC5AC increases tumor heterogeneity (31), which may result from MSI. Increased tumor heterogeneity provides an advantage for escape from immune surveillance. MUCIN5B (MUC5B): Consistent with MUC2 and MUC5AC, hypermethylation of the MUC5B promoter is a major regulatory mechanism for silencing it (32). Intriguingly, intrinsic regions regulate MUC5B (33-35). A 256bp segment of the first intron of the MUC5B contains eight tandem repeat GA boxes located in the GAGGG box, which interact with transcription factors such as Sp1, GATA-1, and AP-2 (35).

Table 1. Mucin expression in human organs

| Organs     | Gel-forming mucins | Transmembrane mucins |
|------------|--------------------|----------------------|
| Esophagus  | MUC5B              | MUC1, MUC4, MUC20    |
| Stomach    | MUC5AC, MUC6       | MUC1, MUC3, MUC13, MUC20 |
| Liver      | MUC2, MUC5AC, MUC5B, MUC6 | MUC1, MUC3, MUC12, MUC20 |
| Pancreas   | MUC5AC, MUC5B, MUC6 | MUC1, MUC3, MUC4, MUC11, MUC13, MUC20 |
| Lung       | MUC2, MUC5AC, MUC5B | MUC1, MUC3, MUC4, MUC12 |
| Reproductive tract | Male: MUC5AC, MUC5B, MUC6 | MUC1, MUC4, MUC12 |
|            | Female: MUC5AC, MUC5B, MUC6 | MUC1, MUC3, MUC17, MUC20 |
| Intestine  | Duodenum: MUC2, MUC6 | MUC1, MUC3, MUC17, MUC20 |
|            | Small intestine: MUC2 | MUC1, MUC3, MUC17, MUC20 |
|            | Colorectum: MUC2    | MUC1, MUC3, MUC4, MUC11, MUC12, MUC13, MUC17, MUC20 |

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MUCIN6 (MUC6): MUC5AC and MUC6 are the major gastric mucins. Whereas MUC5AC is located on the epithelial cell surface, MUC6 is expressed in glandular structures. Staining in a subset of CRC displays exclusively cytoplasmic normal tissue (23). Thus, the expression of tumor cells might result from de novo synthesis by oncogenic signaling. The regulatory mechanism of MUC6 expression is related to the status of promoter methylation, BRAF-V600E mutation, a marker of MCC, as well as MLH1 methylation. Additionally, p53 overexpression shows an inverse association with MUC6 (23). These studies demonstrate a similar regulatory mechanism of gel-forming mucin. Investigation of transcriptional regulatory machinery reported that the Notch signaling pathway increases mRNA levels of the MUC6 and MUC5AC via Hath1, a crucial transcription factor for the Notch signaling pathway, in cancer cell lines (41). MUC6 is frequently associated with the nuclear β-catenin in gastric cancer and younger patients (less than or equal to 40 years old) are more likely to secrete MUC6 (42, 43). Interestingly, similar to MUC5, positive regulation of MUC6 is
observed at the early stage of tumor development, but is diminished at late tumorigenesis, suggesting that MUC6 inhibits tumor cell migration (44). Indeed, MUC6-deficient patients showed short progression-free survival and cancer-specific survival, especially in stage II and III CRC patients (45), implying the involvement of MUC6 in inhibiting tumorigenesis. Conversely, a high level of MUC5AC increased progression-free survival in stage II and III CRC patients.

Together, gel-forming mucins are clustered in chromosome 11p15.5 and share similar regulatory machinery. However, their expression pattern leads to difficulty in targeting an MCC-specific therapeutic strategy. Additionally, they orchestrate diverse physiological events in MCC by communicating either with other signaling pathways or among mucins. Therefore, to resolve these scientific and translational medicine issues, the preclinical animal model of MCC mimicking is likely required.

Transmembrane mucins in cancer

MUC1 (MUC1): MUC1 is a single-pass transmembrane protein with a glycosylated extracellular domain. As a metabolic master regulator (46), MUC1 is mainly expressed in the epithelial cells of the stomach, intestine, and lungs. MUC1 competes with E-cadherin in the cytosol to bind cells of the stomach, intestine, and lungs. MUC1 is mainly expressed in the epithelial with a glycosylated extracellular domain. As a metabolic master regulator, MUC1 causes immunosuppression in MCC by facilitating attachment of cancer cells to the mesothelial lining (86, 87).

MUC4 (MUC4): Like other transmembrane mucins, MUC4 also plays a role in protecting the epithelial surface (70). CRC patients show low expression of MUC4 (99/132 [75%]) (71), which might be mediated by Wnt/β-catenin signaling. Nuclear β-catenin promotes HES1, an antagonist of HATH1 (72). Given the increase of MUC4 by HATH1, CRC might display a low level of MUC4 by Wnt signaling. MUC4 controls cell proliferation, differentiation, apoptosis, and tumor progression via three EGF-like domains, which play as an intramembrane ligand to activate ErbB2 (73). The interaction between MUC4 and ErbB2 activates the downstream pathway of EGF signaling such as PI3K-Akt pathway, which related to proliferation and apoptosis in tumorigenesis. MCC might employ MUC4 for tumor progression instead of Wnt/β-catenin signaling activation.

MUC16 (MUC16): In normal tissue, MUC16, previously known as CA125, expresses in the epithelial lining of several organs (74, 75). It functions as a barrier against the external environment and supports the maintenance of the mucus layer (76). Given high expression in various cancer, MUC16 is extensively employed as a biomarker (77). It is one of the frequently mutated genes, resulting in increased tumor growth and malignancy (78-80). CA125 is a tandem repeated peptide (60-74 repeats of 156 amino acids) of the MUC16, which promotes cancer cell proliferation and resistance to immune surveillance (81). MUC16 inhibits the function of Natural Killer (NK) cells via direct binding to the SigleC-9 receptor of NK cells, resulting in evasion of the innate immune response (82, 83). Also, the interaction may inhibit intimate interactions between NK and cancer cells (84). The interaction between MUC16 and mesothelin, a protein located in the mesothelial lining of the peritoneal cavity, triggers cancer metastasis (85) by facilitating attachment of cancer cells to the mesothelial lining (86, 87).

Because of MUC16-induced JAK-STAT, knockdown of MUC16

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Mucins are complex carbohydrate-protein structures that are highly expressed in various cancers, including Merkel cell carcinoma (MCC). MCC is characterized by high mucin expression, which plays a crucial role in signaling pathway transduction and in the malignant features of MCC cells. Mucins can activate PI3K/Akt signaling to survive under various cytotoxicity conditions. Additionally, they are involved in the development of anti-cancer therapy. This review summarizes the roles of mucins in the tumorigenesis of MCC, discusses the possible applications of mucin-related mouse models, and provides an overview of the past/current clinical trials for MCC.

**CLINICAL TRIALS AND A PRECLINICAL MOUSE MODEL FOR MCC THERAPY**

MCC is mainly characterized by the high expression of mucin, which is categorized into over 20 subtypes. However, their functions in MCC pathology are not completely understood. Additionally, MCC shows malignant features including highly accumulated DNA damage, resistance to cancer therapy, invasive characteristics, and poor prognosis. Nonetheless, the roles of mucins in MCC remain ambiguous, mainly because of the numerous subtypes of mucins, highly complex protein expression, and absence of proper mouse models. Recent studies suggested that MCC exhibits high mucin expression, MSI, frequent mutation of KRAS, BRAF, MAPK, and TOP-1, hyperactivation of the PIK3CA signaling pathway, and increased inflammation. Thus, it is imperative to understand the molecular mechanism for MCC tumorigenesis and to establish MCC mouse models. In this section, we discuss past/current clinical trials for MCC treatment. Moreover, we introduce mucin-related mouse models and a novel mouse model for MCC research.

**Therapeutic targeting of mucin-related oncogenic effects**

**EGFR receptor inhibitors:** As pointed out above, mucins mainly upregulate the EGFR receptor to activate the MAPK pathway. Thus, Cetuximab (anti-EGFR antibody) can inhibit the binding of epidermal growth factor (EGF) and other ligands that are secreted by tumor cells. Gefitinib is the first selective inhibitor of the EGFR tyrosine kinase, which inhibits binding to the adenosine triphosphate (ATP)-binding site of the enzyme. Erlotinib is also referred to as Her1 or ErbB-1. Panitumumab (AbX-EGF) is a recombinant human IgG2 monoclonal antibody, binding to EGFR. Panitumumab competes with the EGF ligand to bind EGFR and shows decreased VEGF production. Although EGF inhibitors show anti-cancer effects, they exhibit various side effects such as acneiform rash, vomiting, diarrhea, skin changes, and loss of appetite.

**Akt inhibitor:** Mucins activate PI3K/Akt signaling to survive under various cytotoxicity conditions. MK2206 (NCT01802320) is an orally available inhibitor of pan Akt (protein kinase B) that inhibits the activity of Akt in a non-ATP competitive manner, resulting in the inhibition of the PI3K/Akt signaling pathway and cell proliferation. Akt contains a Pleckstrin Homology (PH) domain, which binds with high affinity to phosphoinositides including PI(3)P and PI(3,4,5)P3. Although the mechanism of action of MK2206 is not clear, it may interfere with Akt substrates.

**Angiogenesis inhibitors:** Vascular endothelial growth factor (VEGF) plays a crucial role in angiogenesis, lymphangiogene-

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## Figures

- Figure 1: Schematic representation of the PI3K/Akt signaling pathway.
- Figure 2: Inhibitor effects on the PI3K/Akt signaling pathway.

## Tables

- Table 1: Summary of key findings on mucins and their roles in tumor progression.
- Table 2: Clinical trials for MCC therapy.
Table 2. Current and past clinical trials for MCC-related therapy

| Drug                          | Mechanism of action               | Phase                      | Identifier          |
|-------------------------------|-----------------------------------|----------------------------|---------------------|
| MK2206                        | Akt inhibitor                      | Phase2                     | NCT01802320        |
| Alisertib                     | Aurora A kinase inhibitor          | Phase1                     | NCT01923337        |
| Oxaliplatin                   | DNA synthesis inhibitor            | Phase1                     | NCT00005036        |
|                               |                                   | Phase2                     | NCT00060411        |
|                               |                                   | Phase3                     | NCT00217737        |
|                               |                                   |                            | NCT01643499        |
|                               |                                   |                            | NCT01652196        |
| 6,8-Bis(benzylthio)octanoic acid | E1α PDH modulator                 | Phase1                     | NCT0232152         |
| Cetuximab                     | EGFR inhibitor                     | Early phase1               | NCT001000841       |
|                               |                                   | Phase1                     | NCT00835679        |
|                               |                                   | Phase2                     | NCT01198535        |
| Dasatinib                     | EGFR inhibitor                     | Early phase1               | NCT00835679        |
| Erlotinib                     | EGFR inhibitor                     | Phase1                     | NCT00060411        |
| Gefitinib                     | EGFR inhibitor                     | Phase2                     | NCT00052855        |
| Panitumumab                   | EGFR inhibitor                     | Phase2                     | NCT01285102        |
| Gammaseretase inhibitor RO4929097 | Gammaseretase inhibitor            | Phase1                     | NCT01198535        |
| Recombinant interferon gamma  | Macrophage activation factor       | Phase1                     | NCT00002796        |
|                               |                                   | Phase2                     | NCT00002796        |
| Fluorouracil                  | Thymidylate synthase blocking      | Phase1                     | NCT000005036       |
|                               |                                   | Phase2                     | NCT000005036       |
|                               |                                   | Phase3                     | NCT00052855        |
|                               |                                   |                            | NCT0060411         |
|                               |                                   |                            | NCT0217737         |
|                               |                                   |                            | NCT01285102        |
|                               |                                   |                            | NCT01643499        |
|                               |                                   |                            | NCT01652196        |
|                               |                                   |                            | NCT02232152        |
|                               |                                   |                            | NCT02232152        |
|                               |                                   |                            | NCT02235324        |
| Irinotecan                    | Topoisomerase inhibitor            | Phase1                     | NCT00005036        |
|                               |                                   | Phase2                     | NCT00005036        |
|                               |                                   | Phase3                     | NCT00052855        |
|                               |                                   |                            | NCT01285102        |
|                               |                                   |                            | NCT01643499        |
|                               |                                   |                            | NCT01923337        |
|                               |                                   |                            | NCT04088786        |
| Aflibercept                   | VEGF inhibitor                     | Phase2                     | NCT01652196        |
|                               |                                   |                            | NCT02235324        |
| Bevacizumab                   | VEGF inhibitor                     | Phase1                     | NCT000060411       |
|                               |                                   | Phase2                     | NCT001000841       |
|                               |                                   | Phase3                     | NCT00217737        |

tion of DNA and RNA synthesis. RO4929097 is an orally available gamma-secretase (GS) inhibitor, which directly binds to GS and blocks activation of the Notch receptor. These drugs also lead to severe side effects including trouble sleeping, irritability, temporary hair loss, and abnormal taste.

Preclinical mouse model for MCC research

Despite the poor prognosis and metastatic characteristics of MCC (7), the genetic mechanism of MCC development is unknown. Several genetically engineered mouse models (GEMMs) of Muc1, Muc2, Muc5ac, Muc5b, Muc6, and Muc16 have been employed for MCC study (Table 3). However, those GEMMs are highly involved in the maintenance of tissue homeostasis and inflammation without mutations of genes frequently found in the human MCC (KRAS, BRAF, MAPK, and TOP-1) (12-16). It is noteworthy that despite the hyperactivation of the PIK3CA signaling pathway in human MCC, genetic mutations in KRAS, BRAF, MAPK, and TOP-1 do not lead to MCC development in mouse models (105-107). For example, the KRASG12D mouse displays tumorigenesis such as non-small cell lung cancer and pancreatic cancer without MCC development (106).

Recently, it was shown that Cancer-related Regulator of Actin Dynamic (CRAD) is highly mutated in small cell lung cancer, CRC, and melanoma (40, 108). Additionally, the Crad KO mouse initiates tumorigenesis in the pancreas and lung with MCC development (40). Thus, it is highly likely that inactivation of the CRAD gene might be associated with MCC.
### Table 3. Mucin-related GEMMs for MCC study

| Gene  | Allele symbol | Allele attributes | Reported phenotypes                                      | Reference                                      |
|-------|---------------|-------------------|----------------------------------------------------------|------------------------------------------------|
| Muc1  | Muc1<em1Smoc> | Null/knockout     | No abnormal phenotype observed                           | Shanghai Model Organisms Center               |
|       | Muc1<tm1(cre/ERT2)Lcm> | Inducible recombinase | No abnormal phenotype observed                           | Kopinke and Murtaugh, 2010 BMC Dev Biol      |
|       | Muc1<tm1(KOMP)Vcg> | Null/knockout, reporter | No abnormal phenotype observed                           | Velocigene MGI Direct Data Submission        |
|       | Muc1<tm1.1(cre/ERT2)Lcm> | Inducible recombinase | No abnormal phenotype observed                           | Kopinke and Murtaugh, 2010 BMC Dev Biol      |
|       | Muc1<tm1a(EUCOMM)Wtsi> | Conditional ready, null/knockout, reporter | No abnormal phenotype observed                           | Skarnes et al., 2011 Nature                  |
|       | Muc1<tm1a(ENUCOMP)Vlcg> | Null/knockout | No abnormal phenotype observed                           | Skarnes et al., 2011 Nature                  |
|       | Muc1<tm1Gend> | Digestive/alimentary, homeostasis, liver/biliary, neoplasm | No abnormal phenotype observed                           | Spicer et al., 1995 J Biol Chem              |
|       | Muc1<tm1Smoc> | Conditional ready | No abnormal phenotype observed                           | Shanghai Model Organisms Center               |
| Muc2  | Muc2<eey> | Chemically induced (ENU) | Cellular, digestive/alimentary, endocrine/exocrine, hematopoietic, immune, mortality/aging | Heazlewood et al., 2008 PLoS Med            |
|       | Muc2<keny> | Chemically induced (ENU) | Digestive/alimentary, immune                             | The Australian Phenomics Facility at The Australian National University |
|       | Muc2<M1Btlr> | Chemically induced (ENU) | Digestive/alimentary, immune                             | Brandl K et al., MGI Direct Data Submission  |
|       | Muc2<m2Btlr> | Chemically induced (ENU) | Digestive/alimentary, immune                             | Brandl K et al., MGI Direct Data Submission  |
|       | Muc2<m3Btlr> | Chemically induced (ENU), no specific | Digestive/alimentary, immune                             | McAlpine W et al., MGI Direct Data Submission |
|       | Muc2<tm1a(KOMP)Vlcg> | Conditional ready, null/knockout, reporter | No abnormal phenotype observed                           | Skarnes et al., 2011 Nature                  |
|       | Muc2<tm1Avel> | Null/knockout | No abnormal phenotype observed                           | Velcich et al., 2002 Science                 |
|       | Muc2<tm1e(KOMP)Vlcg> | Null/knockout, reporter | No abnormal phenotype observed                           | Skarnes et al., 2011 Nature                  |
|       | Muc2<wnn> | Chemically induced (ENU) | Cardiovascular, cellular, digestive/alimentary, endocrine/exocrine, growth/size/body, hematopoietic, immune, mortality/aging | Robinson et al., 2017 Am J Physiol Gastroint Liver Physiol |
| Muc5ac| Muc5ac<em1Smoc> | Null/knockout | No abnormal phenotype observed                           | Shanghai Model Organisms Center               |
|       | Muc5ac<tm1.1Evns> | Null/knockout | Digestive/alimentary, homeostasis, immune, vision/eye    | Morgan et al., 2021 Nat Commun               |
|       | Muc5ac<tm2a(EUCOMM)Hmgu> | Conditional ready, null/knockout, reporter | No abnormal phenotype observed                           | Helmholtz Zentrum Muenchen GmbH              |
|       | Muc5ac<tm2b(EUCOMM)Hmgu> | Null/knockout, reporter | No abnormal phenotype observed                           | International Knockout Mouse Consortium       |
|       | Muc5ac<tm2e(EUCOMM)Hmgu> | Null/knockout, reporter | No abnormal phenotype observed                           | Helmholtz Zentrum Muenchen GmbH              |
tumorigenesis. The oncogenic mutations and signaling amplification such as KRAS, BRAF, MAPK, and TOP-1, might result from concomitant MCC progression in the MCC-specific tumor suppressor-deficient condition. Therefore, the genetic and molecular basis of MCC development and MCC-specific tumor suppressor needs to be resolved. Currently, anti-MCC therapies, including IR and chemotherapy, are not successful, because of the high resistance of MCC. However, the anti-cancer therapy resistance mechanism of MCC is not understood.

A major reason that these issues have not been successfully addressed was the lack of a preclinical MCC animal model. Mucins interact with each other and utilize another signaling pathway to develop MCC, but the GEMM of each mucin does not mimic the environment of MCC patients. However, the preclinical mouse model for MCC study.

**DISCUSSION**

Metastasis is accompanied by multiple events and requires ideal timing. Further, tumor suppression mechanisms including the immune system, tightly function in the organism to kill cancer cells, thus it is difficult to acquire a wealth of growth factors and nutrients for growth. Hence even malignant tumor cells would often fail to metastasize. The selected malignant tumor cells are more likely to succeed in metastasis. MCC may be the selected cells. Given that MCC maintains enough mucins that could be called a ‘stealth cloak’, MCC can take a stealth strategy and metastasize while being protected by a cloak (Fig. 1). Mucins interact and support MCC efficiently acquire factors necessary for growth and metastasis. Furthermore, mucin provides sanctuary to escape from the surveillance of the immune system. These demonstrate that MCC thoroughly exploits the superior abilities of mucins. For example, mucins are tightly controlled by a regulatory mechanism such as promoter methylation and transcription factor (10, 11). The expression patterns of MUC2 and MUC5 are similar, but the function appears to be independent, which could be utilized by MCC. Transcription factors such as Sp1, commonly regulate the expression of MUC2 and MUC5, but MUC5-induced β-catenin inhibits the expression of MUC2 (43). In the early stage of MCC tumorigenesis, the expression of MUC2 and MUC5 indicates an incompatible pattern. Reduced MUC2 might lead to the inflammatory response that is necessary for MCC development or promote oncogenic mucins. Subsequently upregulated MUC5 might add sup-
pression force for MUC2 via β-catenin. During MCC progression, MUC5 is downregulated as MSI completion, resulting in MUC2 upregulation to escape from immune surveillance through MUC2's protective function. Additionally, following the loss of cell polarity during MCC tumorigenesis, mucins are expressed all over the cell surface and become available to interplay with several growth factor receptors to modulate their downstream signaling.

CRAD stabilizes the cadherin-catenin-actin filament (CCA) complex (40), which means control of cell adhesion and Wnt/β-catenin signaling by CRAD. We have already discussed the role of mucin in cell adhesion and Wnt/β-catenin signaling. The destabilized CCA complex disrupts epithelial cell polarity, which would trigger an inflammatory response and cell proliferation. It is plausible that abnormal polarity, inflammation, and Wnt/β-catenin signaling might foster an oncogenic environment for MCC via elevated mucins. It still unclear how inactivated CRAD increases mucins, but it is clear that a GEMM in which several mucins are simultaneously overexpressed would helpful for future MCC research and the development of anti-MCC therapeutic strategies.

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CONFLICTS OF INTEREST

The authors have no conflicting interests.

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