An alternative way for epithelial-to-mesenchymal transition in colorectal cancer via EIF5A2?

Frank T Kolligs

Epithelial-to-mesenchymal transition (EMT) is a reversible programme which allows the transition between the epithelial and the mesenchymal phenotype in embryonic development, the differentiation of tissues and organs and tissue repair.[1] A direct link between EMT and epithelial stem cell properties has been demonstrated.[2] Aberrant activation of EMT is a trigger for organ fibrosis and the progression and metastasis of epithelial cancers.[1] In colorectal cancer, EMT occurs at the invasive front of the tumour and results in the generation of single migratory cells which have lost expression of the *adherens junction* protein E-cadherin and have gained expression of both vimentin and fibronectin at the same time. Additionally, these cells show activation of the Wnt signalling pathway.[3] At the histopathological level, tumour budding—the detachment of tumour cells from the main tumour—has been described to be closely related to EMT and has been found to be an adverse prognostic factor.[4] Depending on tissue and cell type, EMT is activated by several key pathways, including TGF (transforming growth factor) β, Notch and FGF (fibroblast growth factor) signalling which converge in the stimulation of a group of transcription factors repressing epithelial gene expression.[5]

The gene *EIF5A2* encodes the eukaryotic initiation factor 5A2 and is located on chromosome 3q26, a region frequently amplified in several tumours.[6] EIF5A2 has been shown to induce anchorage-independent growth and xenograft tumour growth of ovarian cancer cells and to enhance cancer cell migration and invasion in cells derived from hepatocellular carcinomas.[7][8] In hepatocellular carcinoma, EIF5A2 has been found to induce EMT and to stimulate rearrangement of the cytoskeleton through activation of RhoA and Rac1.[8] In their paper published in *Gut*, Zhu et al report on the expression and function of EIF5A2 in colorectal cancer.[9] EIF5A2 is reported to be overexpressed in 102 of 229 primary colorectal cancers, and overexpression of EIF5A2 is found to be an adverse prognostic factor. The mean survival of patients with tumours overexpressing EIF5A2 is 64.1 months compared to 83.3 months in patients with tumours expressing normal levels of EIF5A2. Moreover, EIF5A2 was found to be strongly associated with metastatic disease. In experimental studies, the causal role of EIF5A2 in the metastatic potential of colorectal cancer cells was further explored. In colorectal cancer cell lines, EIF5A2 was found to enhance cell motility, invasion and metastasis. In contrast to hepatoma cells this was not mediated by Rho/Rac GTPase activation. By PCR array, among others, the E-cadherin interacting protein α-catenin (CTNNA1) was found to be negatively regulated and the metastasis-associated protein 1 (MTA1) was found to be positively regulated by EIF5A2. At the tumour level, a strong association between EIF5A2 expression with MTA1 expression but not with α-catenin expression was found. Subsequent studies showed that EIF5A2's function to induce invasiveness and EMT and its capability to regulate EMT-associated markers such as E-cadherin, vimentin and fibronectin in colorectal cancer cells was dependent on MTA1. Finally, it could be demonstrated that c-MYC, a known regulator of MTA1, was required for EIF5A2 regulating MTA1 expression. In conclusion, Zhu et al present a rich body of evidence suggesting that EIF5A2 might represent an important factor regulating EMT in colorectal cancer cells via the c-MYC dependent expression of MTA1.

A hallmark of EMT is the loss of expression of E-cadherin encoded by *CDH1*, a crucial suppressor of cancer invasion and progression. The characterisation of E-cadherin regulation during cancer progression has led to the identification of E-cadherin repressors which can be classified into two groups depending on their effects on the *CDH1* promoter[1]: the zinc finger transcriptional repressors SNAI1 and SNAI2 (also known as Snail and Slug, respectively), the zinc-finger enhancer binding protein family members ZEB1 and ZEB2, KLF (Krüppel-like factor) 8, and the basic helix-loop-helix (bHLH) factor E47 bind to and repress the activity of the *CDH1* promoter directly; while Goosecoid, FoxC2 and the bHLH factors Twist and E2-2 repress the expression of E-cadherin indirectly. In addition, c-MYC has been described to indirectly drive the expression of SNAI1.[10] As EIF5A2 is not a direct regulator of E-cadherin, it remains to be established whether EIF5A2's function to repress E-cadherin expression and to induce EMT is mediated via MTA1 only or whether other additional factors are involved. Interestingly, another member of the family of metastasis-associated genes, MTA3, has been found to be a repressor of SNAI1 expression, resulting in the expression of E-cadherin and preservation of the epithelial phenotype, suggesting opposite functions of different MTA family members in the regulation of EMT-associated genes and EMT.[11][12] However, a direct regulation of SNAI1 or another known E-cadherin repressor and master regulator of EMT by MTA1 has not been demonstrated so far.

MTA1 is an integral component of the Mi-2/nucleosome remodelling and histone deacetylation (NuRD) complex and has been shown to be a direct target of c-MYC.[13] It is a critical regulator of the metastatic potential of tumour cells[14] and has been found to be indispensable for c-MYC induced transformation and EMT.[13] Moreover, MTA1 expression has also been associated with HIF-1α mediated angiogenesis and has been proposed as a master co-regulator of carcinogenesis and progression of tumours.[12] In the presence of p53, MTA1 regulates genes involved in antimicrobial and inflammatory response, as well as carbohydrate metabolism, while genes regulated by MTA1 in the absence of p53 are predominantly related to cancer signalling, including direct and indirect interactions with KRAS, epidermal growth factor receptor (EGFR) and vascular endothelial growth factor (VEGF) signalling.[15] Recent data indicate that TGF-β1 induces EMT via stimulating the expression of MTA1.[16]

What are the implications of this study? Activation of invasive and metastasis-promoting capabilities and resistance

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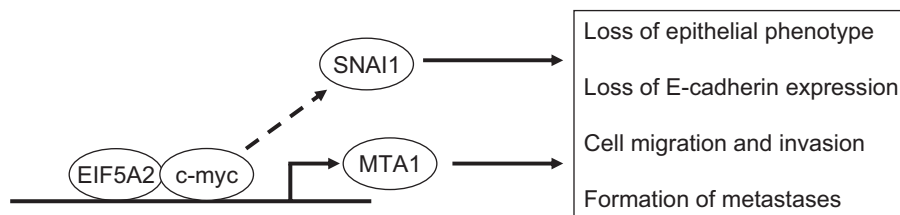
Commentary

Figure 1 EIF5A2 regulates epithelial-to-mesenchymal transition up-stream of MTA1 in colorectal cancer cells. The regulation of MTA1 expression by EIF5A2 is partly dependent on c-MYC. c-MYC is a known indirect regulator of the E-cadherin repressor SNAI1.

to cell death are hallmarks of cancer cells and characteristics of EMT.[17] E-cadherin is the key suppressor of motility and invasiveness in neoplastic epithelial cells. Several transcription factors belonging to different pathways repress the expression of E-cadherin and appear able to orchestrate many steps of the invasion—metastasis cascade. As our picture of this complex and prognosis-determining step is incomplete, the identification of the role of EIF5A2 as an upstream regulator of EMT and metastasis and the description of the EIF5A2-MTA/c-MYC-axis in EMT are important steps forward (figure 1). The further understanding of the network of factors regulating EMT will ultimately allow the development of new pathogenesis-directed preventive and therapeutic approaches. As the expression of EIF5A2 is deregulated in colorectal cancer and is located upstream of MTA1, EIF5A2 may serve as an interesting target for anticancer therapy. However, further understanding of the diverse roles of

MTA family members in homeostasis and disease is required to understand the overall consequences of such an approach.

Competing interests None.

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Too much fat for the gut's microbiota

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The gastrointestinal tract contains a diverse microbial community which is predominantly bacterial and which we refer to as the gut microbiota. For example, the human gut microbiota is assumed to

consist of at least 10^{14} bacteria, composed of more than 1000 species with more than 150 species per individual. Apart from contributing substantial beneficial functions to the host (eg, digestion of indigestible plant polysaccharides and production of short chain fatty acids), the potential of the microbiota to interact with the host and modulate its physiology seems to be tremendous. In addition, many 'environmental' and not yet identified factors might be able to affect and modulate the gut's microbial compo-

sition and functions, with implications for the host.

Recent evidence has linked the development of metabolic dysfunction with our bacteriota, and studies in animals have alluded to the fact that certain microbiotal factors may be associated with the development of diabetes.[1] Whether metabolic dysfunction might potentially lead to or be preceded by a change in the microbiota has not yet been determined. However, in their paper published in *Gut*, Serino and colleagues[2] address this issue by using a mouse model where C57Bl/6 mice with the same genetic background on an identical fat-enriched carbohydrate-free diet develop either diabetes or remain diabetes-resistant.[3] The development of diabetes which appeared in a subgroup of mice was strongly associated with a change in the composition of the gut microbiota.[2] Development of diabetes was associated with

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