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A review on the prognostic significance role of CD44 isoforms in colorectal cancer

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Abstract
D44 isoform switching, a dynamic process involving the interchange between different CD44 variant isoforms, has emerged as a critical regulator of colorectal cancer phenotypic plasticity and therapeutic resistance. This review delves into the complex mechanisms underlying CD44 isoform switching, highlighting the role of transcriptional, post-transcriptional, and signaling pathway regulators in modulating the expression of CD44 standard and variant isoforms. The review further explores the link between CD44 isoform switching and the acquisition of distinct colorectal cancer cell phenotypes, such as increased migratory, invasive, and stem-like properties. Finally, this review discuss the therapeutic potential of targeting CD44 isoform switching to overcome the adaptive capabilities of colorectal tumor cells and improve patient outcomes.

Keywords: Colorectal cancer, CD44 isoform switching, phenotypic plasticity, therapeutic resistance, epithelial-mesenchymal transition, cancer stem cells, targeted therapy

Introduction

Deciphering the Distinct Functions of CD44 Variant Isoforms in Colorectal Tumor Initiation, Growth, and Metastasis

The CD44 standard isoform (CD44s), being the smallest and most widely expressed, differs from its variant isoforms (CD44v), which result from the incorporation of varying combinations of exonic sequences encoding for extracellular domains. Research suggests that the expression patterns of specific CD44 variant isoforms are intimately connected with the progression and clinical outcomes of colorectal cancer. Notably, numerous studies have documented enhanced expression of CD44v6 and CD44v8-10 in colorectal tumours relative to normal colonic epithelial cells. Moreover, high levels of these variant isoforms have been linked to an increased likelihood of lymph node metastasis, distant organ metastasis, and unfavorable prognosis among colorectal cancer patients. Conversely, overexpression of CD44v3 has been associated with improved clinical outcomes, implying that this isoform may possess distinct tumor-suppressive properties.

Table 1: Expression of CD44 Variant Isoforms in Colorectal Cancer

CD44 Isoform	Expression in CRC	Clinical Association
CD44v6	Upregulated	Metastasis, Poor Prognosis
CD44v8-10	Upregulated	Metastasis, Poor Prognosis
CD44v3	Upregulated	Better Prognosis

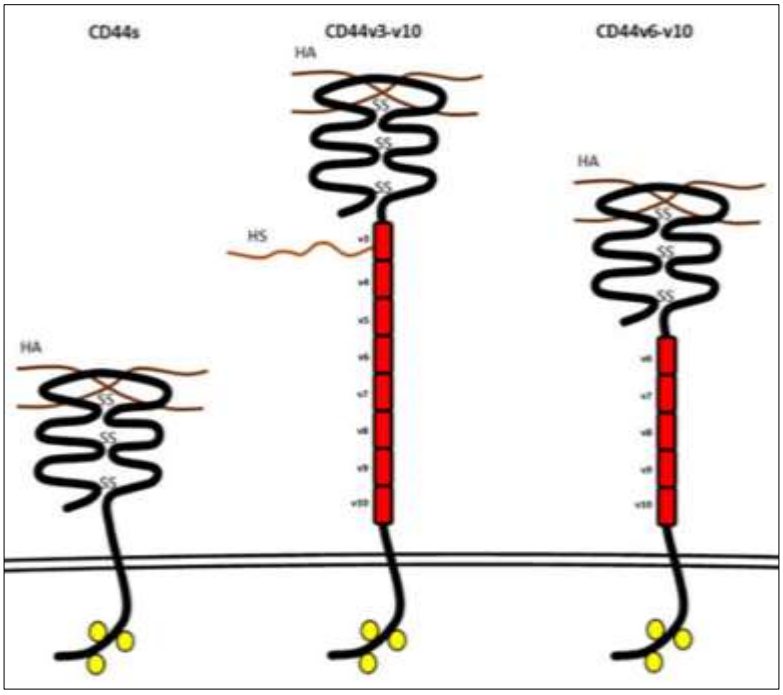

Fig 1: CD44 variant isoforms [7]

The various forms of CD44 protein found in colorectal tumours suggest that each may play a unique role in promoting cancer progression. Specifically, CD44v6 has been linked to enhanced tumour cell migration and invasion by interacting with growth factors and triggering downstream signalling pathways. Furthermore, CD44v8-10 appears to maintain the characteristics of cancer stem cells, which may facilitate tumour initiation and treatment resistance. In contrast, CD44v3 exhibits anti-cancer properties by inhibiting epithelial-to-mesenchymal transition and suppressing metastasis. Notably, this isoform has also been observed to counteract the oncogenic activities of other CD44 variants, indicating a complex interplay among these isoforms within the tumour microenvironment. Considering the disparate and sometimes contradictory roles of CD44 variant isoforms in colorectal cancer, targeted therapies aimed at specific isoforms may provide promising avenues for treatment. For instance, the development of monoclonal antibodies or small molecule inhibitors capable of selectively targeting CD44v6 or CD44v8-10 could potentially disrupt their pro-metastatic functions and lead to improved patient outcomes. Alternatively, strategies designed to enhance the expression or activity of CD44v3 may constitute a viable approach to impede colorectal cancer progression. To inform the rational design of isoform-specific therapeutic interventions, it is essential to further elucidate the regulatory mechanisms governing the expression and functional interactions of CD44 variant isoforms during colorectal carcinogenesis.

CD44 Isoform Switching

A Critical Regulator of Colorectal Cancer Phenotypic Plasticity and Therapeutic Resistance

The dynamic regulation and interchange between different CD44 variant isoforms, a process known as "CD44 isoform switching," has emerged as a critical driver of colorectal cancer progression and therapeutic resistance. This phenomenon underscores the remarkable phenotypic plasticity exhibited by colorectal tumor cells, which can adapt and survive under diverse micro-environmental conditions and therapeutic pressures [12].

Mechanisms of CD44 Isoform Switching in Colorectal Cancer

CD44 isoform switching is a complex and highly regulated process that is influenced by a variety of factors, including transcriptional and post-transcriptional mechanisms, epigenetic modifications, and signaling pathways [13]. As shown in Table 2, several key regulators of CD44 alternative splicing have been identified in the context of colorectal cancer.

Table 2: Regulators of CD44 Isoform Switching in Colorectal Cancer

Regulator	Mechanism of Action	Effect on CD44 Isoforms
Epithelial-Mesenchymal Transition (EMT) Transcription Factors	Transcriptional regulation of CD44 splicing factors	Promotes expression of CD44 variant isoforms
Hypoxia-Inducible Factor 1α (HIF-1α)	Transcriptional regulation of CD44 splicing factors	Promotes expression of CD44 variant isoforms
microRNAs (e.g., miR-23b, miR-671)	Post-transcriptional regulation of CD44 splicing factors	Suppresses expression of CD44 variant isoforms
Protein Kinase C (PKC) Signaling	Phosphorylation and activation of CD44 splicing factors	Promotes expression of CD44 variant isoforms

These regulators can orchestrate the dynamic shifts in CD44 isoform expression, leading to the acquisition of distinct cancer cell phenotypes that are associated with increased migratory, invasive, and stem-like properties [14].

The ability of colorectal tumor cells to switch between CD44 standard (CD44s) and variant (CD44v) isoforms is closely linked to their capacity for phenotypic plasticity, which is a hallmark of aggressive and treatment-resistant cancers. For instance, the upregulation of CD44v isoforms, such as CD44v6 and CD44v8-10, has been associated with the epithelial-mesenchymal transition (EMT) process, enabling cancer cells to acquire a more migratory and invasive phenotype [15].

Conversely, the expression of CD44s has been linked to a more proliferative and epithelial-like state, while the co-expression of both CD44s and CD44v isoforms has been observed in colorectal cancer stem-like cells [16]. This dynamic interplay between CD44 isoforms allows colorectal tumor cells to adapt to changing microenvironmental cues and therapeutic pressures, ultimately promoting tumor growth, metastasis, and therapeutic resistance. Given the crucial role of CD44 isoform switching in regulating colorectal cancer phenotypic plasticity and therapeutic resistance, targeting this process has emerged as a promising therapeutic strategy. Several approaches are currently being explored, including, Inhibition of CD44 splicing regulators: Disrupting the activity of transcription factors, signaling pathways, and epigenetic modifiers that control CD44 alternative splicing can potentially limit the expression of pro-tumorigenic CD44 variant isoforms [17,18].

Isoform-specific CD44 targeting: Developing monoclonal antibodies or small-molecule inhibitors that selectively target specific CD44 variant isoforms, such as CD44v6 or CD44v8-10, may disrupt their pro-metastatic and stem-like functions [19, 20]. Modulation of microRNA regulation and enhancing the expression of microRNAs that suppress CD44 variant isoform expression, such as miR-23b and miR-671, could potentially restrict the phenotypic plasticity of colorectal tumor cells [21].

By targeting the dynamic process of CD44 isoform switching, these innovative therapeutic approaches aim to overcome the adaptive capabilities of colorectal cancer cells, potentially improving patient outcomes and reducing the risk of disease recurrence and metastasis.

From the Cell Surface to the Metastatic Niche

Unraveling the Multifaceted Impacts of CD44 Isoform Expression in Colorectal Carcinogenesis

The dynamic regulation and interchange between different CD44 variant isoforms, a process known as "CD44 isoform switching," has emerged as a critical driver of colorectal cancer progression and therapeutic resistance. This phenomenon underscores the remarkable phenotypic plasticity exhibited by colorectal tumor cells, which can adapt and survive under diverse microenvironmental conditions and therapeutic pressures [22]. CD44 isoform switching is a complex and highly regulated process that is influenced by a variety of factors, including transcriptional and post-transcriptional mechanisms, epigenetic modifications, and signaling pathways [23]. Several key regulators of CD44 alternative splicing have been identified in the context of colorectal cancer. Epithelial-Mesenchymal Transition (EMT) Transcription Factors, such as Snail, Slug, and Twist, have been shown to promote the expression of CD44 variant isoforms by transcriptionally regulating the expression of splicing factors involved in CD44 alternative splicing [2, 3]. Similarly, the transcription factor Hypoxia-Inducible Factor 1α (HIF-1α), which is activated in response to hypoxic conditions within the tumor microenvironment, can also induce the upregulation of CD44 variant isoforms [24]. In addition to transcriptional regulation, post-transcriptional mechanisms involving microRNAs (miRNAs) have also been implicated in the control of CD44 isoform switching. For instance, miR-23b and miR-671 have been reported to suppress the expression of CD44 variant isoforms by targeting the splicing factors that regulate their inclusion [25, 26].

Furthermore, signaling pathways such as Protein Kinase C (PKC) signaling can also influence CD44 isoform switching by modulating the activity of splicing factors through phosphorylation events [27]. These diverse regulatory mechanisms orchestrate the dynamic shifts in CD44 isoform expression, leading to the acquisition of distinct cancer cell phenotypes associated with increased migratory, invasive, and stem-like properties. The ability of colorectal tumor cells to switch between CD44 standard (CD44s) and variant (CD44v) isoforms is closely linked to their capacity for phenotypic plasticity, which is a hallmark of aggressive and treatment-resistant cancers. The upregulation of CD44v isoforms, such as CD44v6 and CD44v8-10, has been associated with the epithelial-mesenchymal transition (EMT) process, enabling cancer cells to acquire a more migratory and invasive phenotype [28, 29]. Conversely, the expression of CD44s has been linked to a more proliferative and epithelial-like state, while the co-expression of both CD44s and CD44v isoforms has been observed in colorectal cancer stem-like cells [30]. This dynamic interplay between CD44 isoforms allows colorectal tumor cells to adapt to changing micro-environmental cues and therapeutic pressures, ultimately promoting tumor growth, metastasis, and therapeutic resistance.

Given the crucial role of CD44 isoform switching in regulating colorectal cancer phenotypic plasticity and therapeutic resistance, targeting this process has emerged as a promising therapeutic strategy. Several approaches are currently being explored, including: Inhibition of CD44 splicing regulators: Disrupting the activity of transcription factors, signaling pathways, and epigenetic modifiers that control CD44 alternative splicing can potentially limit the expression of pro-tumorigenic CD44 variant isoforms [31, 32].

Isoform-specific CD44 targeting: Developing monoclonal antibodies or small-molecule inhibitors that selectively target specific CD44 variant isoforms, such as CD44v6 or CD44v8-10, may disrupt their pro-metastatic and stem-like functions [13,14]. Modulation of microRNA regulation: Enhancing the expression of microRNAs that suppress CD44 variant isoform expression, such as miR-23b and miR-671, could potentially restrict the phenotypic plasticity of colorectal tumor cells [33]. By targeting the dynamic process of CD44 isoform switching, these innovative therapeutic approaches aim to overcome the adaptive capabilities of colorectal cancer cells, potentially improving patient outcomes and reducing the risk of disease recurrence and metastasis.

Conclusion

CD44 isoform switching plays a pivotal role in shaping the phenotypic diversity and therapeutic response of colorectal cancer. The dynamic regulation of CD44 variants, influenced by transcriptional, post-transcriptional, and signaling mechanisms, underscores its significance in driving tumor progression, metastasis, and resistance to treatment. The distinct functions of CD44 standard and variant isoforms highlight their potential as targets for innovative therapeutic strategies aimed at disrupting cancer cell plasticity and improving patient outcomes. Further

research into the regulatory networks governing CD44 isoform switching is essential to advance our understanding and development of targeted interventions in colorectal cancer therapy.

Conflict of interest

No potential conflict of interest relevant to this manuscript was reported.

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