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CD44 cleavage product CD44-intracellular domain regulates gene transcription and tumorigenesis

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Abstract

CD44 is a multifunctional transmembrane glycoprotein that is expressed in many cancers and can regulate invasion and metastasis. CD44 can interact with a multitude of ligands to promote metastasis and invasion. CD44 is also a known cancer stem cell marker. Due to alternative splicing, CD44 can exist in multiple isoforms besides standard CD44 isoform. Recent studies have shown that CD44 can be proteolytically cleaved into CD44-intracellular domain (ICD). Specifically, this cleavage product ICD translocates into the nucleus to activate transcription of a variety of genes that are critical to inflammation, cell survival, glycolysis, and cancer metastasis.

***Keywords**: Cancer, Metastasis, CD44, CD44-ICD, Transcriptional Factor.*

CD44 – Transmembrane Glycoprotein

CD44, a cell surface receptor for osteopontin (OPN) and hyaluronic acid (HA) and other ligands is known to play critical roles in cancer cell migration, invasion, and tumor growth [1–6]. Multiple isoforms of CD44 exists due to the insertion of alternative exons at the extracellular domain site [5]. CD44 is expressed ubiquitously and distributed widely in fetal and adult tissues with varying degrees of expression [7–9].

CD44-Intracellular Domain (ICD)

CD44 can undergo sequential proteolytic processing to create an intracellular domain (ICD) fragment that can translocate into the nucleus to regulate the expression of a few genes [10–18]. This sequential cleavage of CD44 to generate the ICD fragment can be first mediated by metalloproteases (MMPs) at the ectodomain portion to create a fragment known as CD44 extracellular truncation (EXT). Sequentially, cleavage by γ-secretase at the transmembrane domain generates the CD44-ICD fragment. This fragment is capable of translocating into the nucleus to regulate gene transcription [13, 18].

CD44-ICD Transcriptional Factor

CD44-ICD has recently been shown in several cancers as the main factor responsible for tumorigenic potential of the cells. Specifically, in prostate cancer, CD44-ICD was found to be associated with the master regulator of osteoblastogenesis RUNX2 to mediate the transcription of matrix metalloproteinase 9 (MMP-9) gene [24]. Additionally, CD44-ICD interacts with a novel consensus sequence in the promoter region of the MMP-9 gene to regulate its expression. Furthermore, CD44-ICD activates multitudes of genes involved in cell survival, tumor invasion, glycolysis, etc. in breast cancer cells [11]. Cleavage product CD44-ICD has also been shown to support the activation of stemness factors Nanog, Sox2, Oct4, thereby promoting tumorigenesis of breast cancer [19]. In thyroid cancer cells, CD44-ICD has been shown to trigger activation of the CREB transcription factor thus sustaining proliferative signaling [10]. Studies have also shown that CD44-ICD has the capability of regulating the transcription of CD44 itself [14]. In other cell types like chondrocytes, CD44-ICD release has been shown to exert a competitive effect on full-length CD44 function [20].

Conclusion

The multifunctional receptor CD44 is involved in a variety of functions ranging from aggregation to migration and metastasis. CD44 can interact with different ligands to elicit many cellular functions. Emerging studies have analyzed the role of CD44-ICD in mediating and promoting tumorigenesis. CD44-ICD upregulates and activates genes involved in invasion, migration, and tumorigenesis. Taken together, CD44-ICD could be a therapeutic target in cells, including cancer cells that express CD44.

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