Mintage Journal of Pharmaceutical & Medical Sciences

Vol 9, Suppl 1 Jan-Mar, 2020 ISSN: 2320-3315

Research Article

CD44 AS A TUMOR MARKER DIAGNOSTIC, THE ROLE IN CANCER PROGRESSION

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Received - 04.11.2019; Reviewed and accepted - 10.12.2019

ABSTRACT

Objective: In the last decade, the cellular protein CD44 is studied in relation to carcinogenesis. The "nonkinase transmembrane glycoprotein" was overexpressed in many type of cells especially in cancer cells. The epithelium origin tumor expresses the CD44 in many isoforms and known as variants, most of the isoforms correlation with specific cells of cancer. it can show an alternative distributed variant which thoughts that plays a major role in cancer progression or development. Hyaluronic acid a main primary ligand for "CD44" binding and activating "CD44", as a result, activates pathways of "cells signaling" and induce "cell proliferation", increase survival cells enhances cellular motility as well as modulate cytoskeletal change. This binding is thought to regulate another biological process within a cell. within the tissue, the cells either interact within "intracellular matrix" or within a cellular junction, the adhesive molecules, CD44 enable the communication from cell to cell signaling transduction.Till now uncertainty known regarding exact mechanisms of "CD44 participates" in the cancer growth or the inflammation response, in current data we focus on structure as well as CD44 function prevalence in tumorigenicity, the regulation of "CD44 expression" and "CD44 potential" targeted CD44 in cancer therapeutic. We will discuss many examples of tumors in this review and consider cells tumorigenic behavior which expresses the highly CD44 as the earlier marker of "neoplastic stem cell proliferation".

Keywords: CD44, Cancer, Tumorigenicity, therapeutic carcinoma.

INTRODUCTION

CD44 is one of non-kinase family, with an 85-200 KDa of molecular weight. Single vast transmembrane glycoprotein which expresses on embryo stem cell and on different levels of another cell type that included the connective tissue as well as the bone marrow [1, 2].

In human cells "CD44" genetic composition found the "CD44 gene" is located at short arm on chromosome 11.while, it is consists of 50 KB of human DNA, whereas, "CD44 chromosome" is consists of twenty exons, twelve from them played a major role on splicing. In the other hand the exons (1-5) encode the constant area in an "extracellular domain", furthermore, exons (6-15) encoded for changeable sides of "extracellular domain". The extracellular domain proximal area is encoded by (exon 16 and 17).whereas, Exon (18) is invariable exon which encoding hydrophobic area as well as first three amino acids in "CD44 cytoplasmic tail". Exon (19) is wealthy in adenine plus thymine, which is an untranslated area that thought to produce long three amino acids with "not short cytoplasmic tail", Exon (20) participate to generate "CD44 long cytoplasmic tail"[3].

The CD44 expression is upregulated in a subpopulation of the cells of cancer also can recognize as "molecular marker" in stem cells of cancer [4], whereas, it's encoded from twenty exons in humans, ten exons fixed on all the isoforms. A criterion CD44 form is encoded via 10 permanent exons[5].

The transporter studies are widely expressed on all cell types of the body. The cell surface glycoprotein is found in epithelial, leukocytes, fibroblasts, neuroectodermal, and mesodermal cell, The distribution assists the realization, and as well institute in numerous stem cells of cancer. The spread in cancer cells catches the interest to on concentricity the connection of molecular beginning of the tumor evolution.

Pathological role of CD44

In a variety of diseases, CD44 is highly expressed. It can be found in cancerous, auto-immunological diseases and inflammatory. Some scientists investigated CD44 isoforms to detection an accurate relationship between specific cancers and CD44, correlate specified isoforms together with a confirmed form of CSC and inflaming immunological reaction. It was established at many tumor malignancies, the CD44 levels were higher, chronic inflammatory reaction, and also autoimmune dysfunction.

The "CD44s" and the "isoforms" clinicopathological impacts of preferring tumorigenesis are suggested of CD44 probably a molecular base on the treatment of cancer [6]. while a certain function in "CD44" of preserving stemness with the stem cells of cancer functions in tumor renewal that subsequent the treatment which proposes that "CD44" as well the main prognostication marker.

The therapeutic strategically which target "CD44" and reduced it's express was at diverse phases in clinical expansion[7,8,9]. The strategy may contain CD44 neutralizing antibody as well as tumor delivery of shRNA, ectodomain mimics, and also an aptamers [8,10,11]. From these, the main region of investigations is attend defined the "functional CD44 isoforms" role in cancer and also determines the prospect benefit for targeting the "CD44 isoform" or it's signaling pathway of cancer therapies.[12].

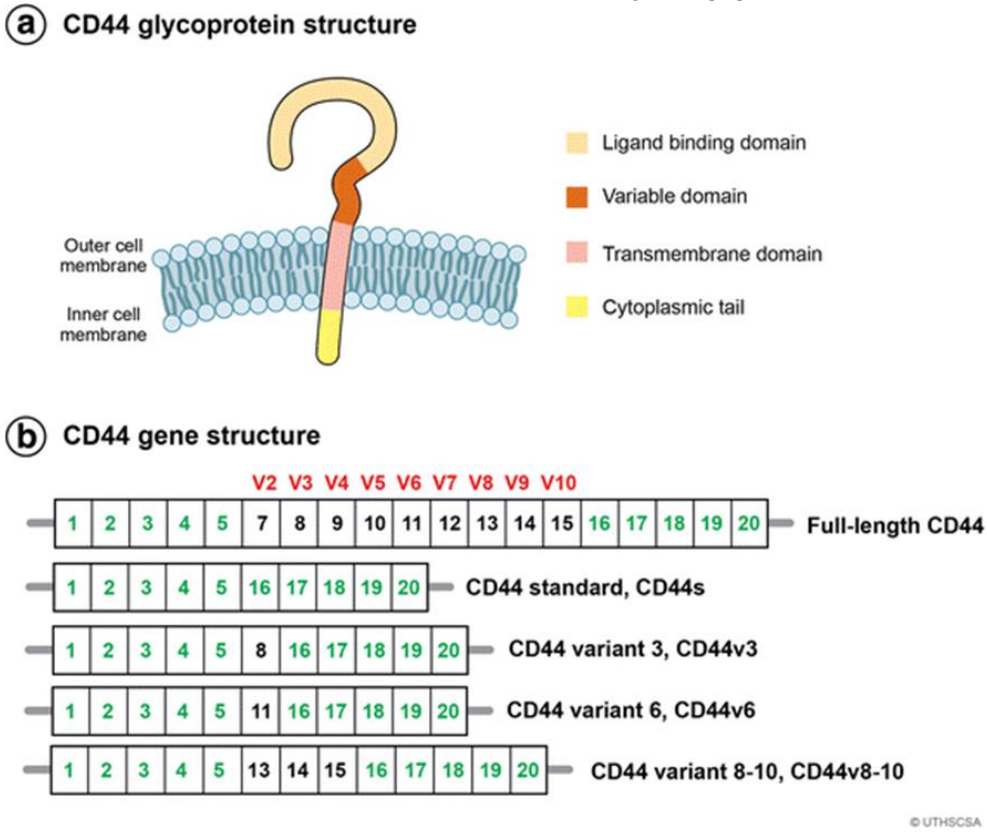
Immune response mediated in a diversity of cellular and dissolvable elements. T-lymphocyte, as well as dendritic cells, are develope in CD44 expression. CD44 implicated on a rearranging of cytoskeleton and adherence of T- lymphocyte. signaling pathway of T - cell receptor initiated from CD44 and associated to tyrosine phospho-kinases 'p56lck/p59fyn' [13]. at a dendritic cell, cross-linking of CD44 and monoclonal antibody can promote dendritic cell accumulation and maturation. also increases the excretion of cytokine-like interleukin (IL)-8, IL-1beta, tumor necrosis factor alfa(TNF). Treating of a dendritic cell to anti CD44mAb inhibits T-cell activities in vitro, engaging of 'major histocompatibility (MHC)' peptide with (TCR) mediated out of 'adenomatous polyposis coli (APC)' cell junction[14]. This well-arranged junction is mentioned to immunological synapse. The immune synapse drafts CD44 through allogeneic engaging among T cell and dendritic cell, that's why attend activation in T cell[15]. CD44 engaging to the ligand HA can regulate the immune/inflammatory responses. The main interleukin IL-5 in charge of eosinophilic inflammatory asthma.it can be promoting CD44 expression of eosinophils and murine B cell in humans [14]. The CD44 can also promote guided of CSC on various kinds of solid tumors, so as in breast cancer as well as prostate cancers.

and mediate leukemic stem cell sin guiding to the niches. The expression of CD44 is a drop of a set while CSCs are inserted to cancer suppressor elements like “p53 and microRNA 34a” [13,16].

CD44 function and Structure

The “non-kinase proteoglycan” transmembrane, which is single/chain glycoprotein that encoded via one gene existing at ‘chromosome 11’ on humans, while in mice at ‘chromosome 2’. A gene of CD44 included about ‘19 exons’ in humans and ‘20 exons’ in mice. In humans, the ‘exon 6’ homolog or different 1 is not organized [17]. Both of the first-five, so as, the last-five exons are steady as well as encode shortest “CD44 isoform”, ‘85–95 kDa’ known as CD44 standard “CD44s”. The 9 exons on the middle may alternatively be tied or assemble with 10 exons consists in ‘CD44 standard isoform’, then mentioned to the CD44 variant isoforms “CD44v”.

CD44v isoforms integrated as ‘single variant exon’ or/ as joined to the other variant exons which sign for a peptide that existing in a juxtamembrane domain; encoded CD44 peptide may be either adaptor by “N- and O-linked” glycosylation, glycosaminoglycanation by the accession of ‘heparin sulfate or chondroitin sulfate’ [18,19]. CD44 is an extracellular domain, the membrane-proximal aerea/ transmembrane domain, cytoplasmic tail. The explanation of CD44 gene shows “CD44s and CD44v” exons, functional domains, peptides position of coded by variant exons Figure. 1. [20].



Figure(1): CD44 protein/gene structure.(A) The 4 domains CD44 glycoprotein given with corresponding colors. the ligand obligated domain, the changeable domain, a transmembrane domain, while a cytoplasmic tail.(B) CD44 encoded via twenty exons in mouse and nineteen exons in humans. Whereas, exon 6 coding to “CD44v1” lacking in humans. The green exon ever expressed as “CD44s”, up to 9 exons differents may be inserted by alternate spliced. Full length of (CD44, CD44s, CD44v3, CD44v6, as well as CD44v8-10) also shown schematically.

CD44 roles in tumorigenicity

CD44 can be activated and modulate a number of cells signaling network which plays a main function on mediates tumorigenic immovables for tumor cells (table 1), that leads to tumor ascertainment, chemoresistance, metastasis.it is thought that CD44 is responsible to the adaptive plasticity of cancerous cells [21]. Cancer cells adaptive plasticity is an expression that explains how the phenotype alteration in restraint to microenvironment which supplies cancer cells, eclectic growth, the existing capabilities as well; (EMT) a way of adaptive plasticity, it is an example of the transposition from epithelial to mesenchymal-like phenotype. this cell shows a boost in motility, much invasive, mostly further impedance to apoptosis [22]. The metastatic lesions expansion is probably to require that cells resit the epithelial state over inverse mesenchyme to epithelial transition “MET”, which considered to favor tumors get along and growing cancer cells at the metastatic site [23].

The CD44 functional role in the “EMT” was examined on varied tumors. At cells of colon carcinoma, the mesenchymal phenotype correlating to the boost of CD44 and strike in CD44 showed a reduction in “EMT” phenotype. CD44 overexpression down-regulate (E-cadherin) express, up-regulated (N-cadherin, α-actin, vimentin, fibronectin, and inhibited the formation of membrane-associated E-cadherin-β-catenin) complex that results on “cell invasion and migration”. CD44 knock-down cells have shown a remarkable reduction invasion with migration, over-expressing cells of CD44 display safely boost cell emigrating as well as invasive capability [24].

CD44s isoform can promote “EMT” while the knock-down prevents “EMT”. reexpression of CD44s totally saved the destroyed “EMT” phenotype on cells of CD44 knockdown with reduction the expression of epithelial marker (E-cadherin with occluding) but boost the expression of mesenchyme markers (N-cadherin and vimentin); “ESRP1” adjusts the CD44 alternative splicing to prefer the exon inclusion for CD44 isoforms while then require to order “CD44v” expression [25]; “ESRP1” can inspect CD44 post-transcriptional via spending different effects in protein interpretation via “5′-UTRs” of mRNAs [26]. Knocking-down the “ESRP1 in CD44v” expressing cells which result on isoform transformation to “CD44s”, then command to lung colonization repression [27].

We recently were deserved for dissociating cells of cancer at a base of “CD44” level expression employment the flowing of cytometry [28]. The Mouse at orthotopic implant of “CD44s” raise cells to form a tumor very fastly, slowly expansion impedance for gemcitabine, furthermore, cancers of CD44 low expression cell pull long-term till expand and maintain sensitiveness for gemcitabine through the prolonged term. whereas, tumor constructed of “CD44 high EMT” chemoresistant cells displayed expressing from “CD44v” suggestion the dynamic switch of “CD44 isoforms” through the formation of the tumors;” CD44s can act an important role in “EMT” as well as tumor prevalence and “CD44v” can acts in tumor contriving and growth [28].

Table 1. CD44 as a cancer marker in different types of cancer

Type of Cancer	Type of CD44	The references
Head and neck	Pan-CD44+,CD44v3	[38]
Breast	CD44v+	[39]
Leukemia	Pan-CD44(High)	[40]
Intestinal-Colon	Pan-CD44+,CD44v2+,v6+,v9+	[41,42]
Pancreas	CD44s+	[43,44]
prostate	Pan-CD44,CD44v6	[45,46]

CD44s:standard, CD44v:variant, pan-CD44:all CD44 isoforms

CD44 with head and neck SCC

The grade of CD44 was lead to increased at head and neck SCC, the cell line as well as the higher CD44 levels leads to a great increase at cells immigrant [29]. CD44 isoform transfection for the non-expressing head and neck SCC cell line results at the boost tumor cell immigrant. Anti CD44 antibodies treatment at these cells effected decreased in vitro proliferation as well as cisplatin resistance [30].

CD44 and Breast cancer

A cell of breast cancer shows marked heterogeneity, also the variety through breast cancer although during tumors. Breast cancer cells examining by the mechanism known “ Gene Expression” sidelong indicate the cell of cancer shows the different people in cell subtype. CD44 abnormally expressed in the cells of breast cancer.[31]In previous 10 years, clinical researches have shown a cause of increasing the CD44 expression established in cell surface that separated of patients with breast cancer. closely researches refer that is no statistical significance among CD44 overexpression with growth and metastasis of breast cancer. whereas, another study reported the correlation presence among an anomaly of CD44 in breast tumor cells as well as mesenchymal such phenotype. It is also has been proposed that CD44 is the basal cell line that may be purpose like a sign of poor breast cancer warning cases [21].

Leukemia with CD44

The ordinary hematopoietic propagation cells at all grown-up occur on bone marrow in different additional maturation by another organ. Previous researches of CD44[18]suggests the regulation of normal hematopoietic cell proliferation by CD44. The treatment in vitro in long-dated bone marrow culture cells by anti CD44 antibody through the differential phase can show reduce on several forward cells. CD44 acts as major part in bone marrow in myeloid cell proliferative. According to that, it can be explained that CD44 mediates many microenvironmental functions of the bone marrow[19].

CD44 with intestinal-colon cancers

The CD44 diverse (4-10) in intestinal carcinoma well organized in very expressed on the mice intestine carcinoma. In human intestinal cancers, standard CD44 isoform is not isolated yet; whereas, some CD44 variants were enormously detected on the same cancers. Another splicing of mRNA CD44 makes some different of CD44, that produces as a complicated to investigators for identifying an accurate function of any isoform on intestinal carcinoma[32] all researchers agree on the CD44 tumorigenicity, the exact CD44 function in tumor cell is not clear[33].

CD44 and Pancreas carcinoma

Pancreas cancer of human tissues expressed different isoforms of CD44. The “CD44v6” is generally considered CD44 unlike on pancreas carcinoma. Increase the expression of “CD44v6” on pancreas cancer can act an important role on the metastasis [34]. Several previous kinds of research at human pancreatic carcinoma suggested that “CD44v” may be usage as a good marker at clinical notice. [35].

CD44 and Prostate cancer

Approximately about 148 prostate tissues raised of prostatic carcinoma, high-level prostate intraepithelial neoplasia, while, benign prostatic hyperplasia are immunostained with CD44. CD44 highly grade expression can be spotted on 42% in prostate cancer, 57% high grade prostatic, and 42% benign prostate hyperplasia, it suggested that expression of CD44 was not correlated with prostate cancer malignant stage [36]. The CD44 isoforms roles were inspected correlated with prostatic carcinoma in previous studies. In the localized prostate cancer, CD44s is underexpressed , also all different isoforms are overexpressed. The CD44 highly expression separately correlation to the best rate of repetition free duration [37].

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