The Role of Cluster of Differentiation 74 in Cancer and Cancer Immunomodulation

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ABSTRACT

In normal cells cluster of differentiation 74 (CD74) acts as a chaperone of human leukocyte antigen (HLA)-DR by formation of a trimetric structure. In the lack of tumor presence most antigen presenting cells are expressed. However, recent data suggests that CD74 is major link between proinflammatory responses and tumorigenesis but that detailed mechanisms are not fully understood. CD74 is also thought to be involved in signalling pathways via macrophage migration inhibitory factor (MIF) and CD44; controlling the proliferation and apoptosis of cancer its capability to interact with other signaling cells. The role CD74 as an accessory signal receptor on surface and molecules presents CD74 as a crucial therapeutic target for the treatment of cancer. This review will discuss the role of CD74 in several aspects including antigen presentation, cancer immunomodulation as well as the interaction of CD74 along with MIF and CD44.

The overall aim of this review is to translate the recent outcome from the previous study to the clinical level and to study the expression and the role of CD74 in human breast cancer in Saudi population. Comparison between normal people and patients could be applied. We are also planning to link the level of CD74 expression to different stage of breast cancer so CD74 could potentially be used as a 'biomarker signature' to monitor different stages of breast cancer.

Key Words: Antigen presentation, Invariant chain, IFN-γ, lipopolysaccharide (LPS), Tumorigenesis

INTRODUCTION

Structure of cluster of differentiation 74

In humans, the gene that encodes the CD74 or invariant chain (Ii) molecule is located on chromosome 5q32 (Yamamoto, 1985; Liu and Lin, 2014). Jones and his colleagues were the first to recognize the Ii protein in 1979, specifically when the MHC class α chain and Ii was separated in 2D-gels. In spite of this, in 1989 it was discovered that Ii has a vital role in antigen presentation through persuading the expression and peptide loading of MHC class II molecules (Badve *et al.*, 2002). In 1995, the name CD74 was given to Ii by 'Leukocyte Typing Workshop' (Landsverk *et al.*, 2009). CD74, also known as invariant chain, Ii or MIF receptor, is classified as a type II transmembrane glycoprotein that is expressed on antigen presenting cells and has diverse immunological functions (Burton *et al.*, 2004; Stein *et al.*, 2007; Beswick and Reyes, 2009). CD74 is post-translationally glycosylated and exists in various isoforms. There are four isoforms of CD74 in human beings, P33, P35, P41 and P43. Via alternative splicing of the invariant chain (Ii) transcript where the P41 isoform has an extra exon, (exon 6b) these isoforms can be differentiated. However, the most common isoform (P33) has a molecular weight of 33 kDa (Landsverk *et al.*, 2009; Beswick and Reyes, 2009). The structure of CD74 (shown in Figure 1) consists of a short an NH2-terminal cytosolic tail of 30 amino acids, intracytoplasmic residues (IC), a 26 amino acid hydrophobic transmembrane region (TM) and 160 amino acid extracytoplasmic domain containing two N-linked carbohydrate chains (EC) (Stein *et al.*, 2007; Landsverk *et al.*, 2009; Shachar and Haran 2011; Gil- Yarom *et al.*, 2014). CD74 is synthesized on the rough endoplasmic reticulum in same manner as MHC class II molecules despite the genes of these molecules being located on different chromosomes (Badve *et al.*, 2002).

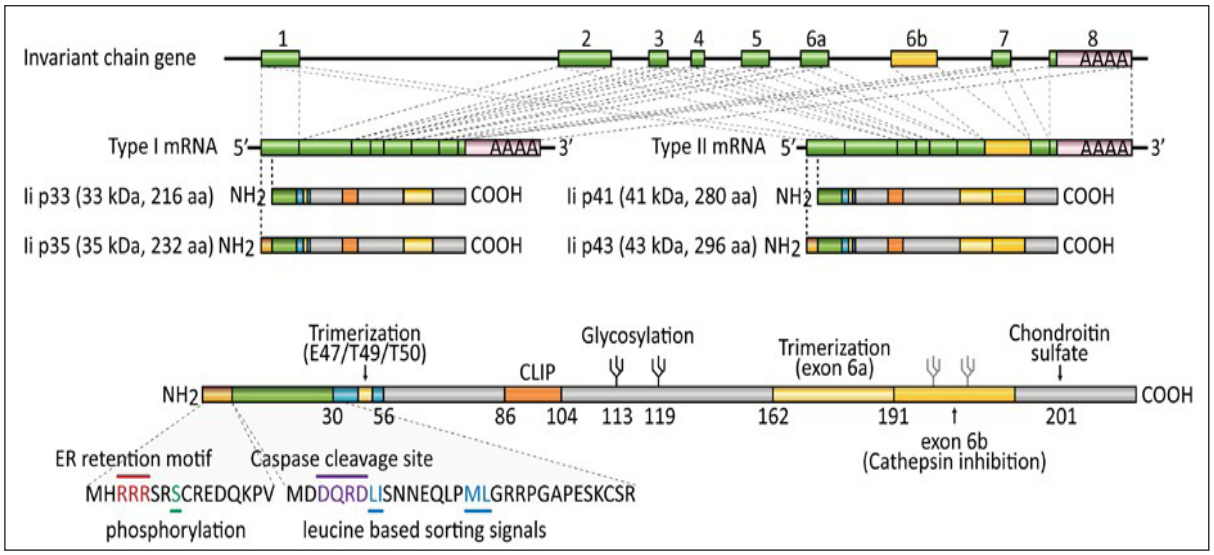

Figure 1: Schematic diagram of gene and protein structure of CD74.

The corresponding gene of the invariant chain (Ii) consists of nine exons. The p33 and p35 forms of Ii, both encoded by eight exons, differ by 16 N-terminal residues as a result of alternative translation initiation. The p41, encoded by nine exons, is generated by alternative splicing of a common pre-m-RNA. The exon 6b in p41 and p43 encodes a cysteine rich stretch of 64 amino acids near the C-terminus. All isoforms contain at least two N-linked and two O-linked glycosylations. Adapted from (Strubin *et al.*, 1986, Gregers *et al.*, 2003).

The function of CD74

The most well-known function of CD74 is its ability to associate with MHC class II α and β chains, directing the transport of the αβIi complex to the endosome and lysosome (Pyrz *et al.*, 2010). Specifically, the role of CD74 in antigen presentation has been divided into three main functions. Firstly, CD74 acts as a chaperone that is responsible for stabilizing nascent human leukocyte antigen (HLA)-DR αβ-heterodimers by formation of a trimetric structure. Secondly, by means of various sorting and internalization signals in its N-terminal cytoplasmic tail, CD74 targets HLA-DR molecules to subcellular compartments. Thirdly, CD74 prevents loading of antigenic peptides into the groove of HLA-DR molecules outside endosomes/lysosomes through a stretch called CLIP (Class II-associated Invariant chain Peptide) (amino acids 91-99) (Moldenhauer *et al.*, 1999). CD74 is evolving as a more effectual molecule beside its eminent functions of regulating class II MHC trafficking. Numerous studies have elaborated that cell-surface expression of CD74 is not always reliant on class II MHC (Wilson *et al.*, 1993; Beswick and Reyes, 2009). In this context, CD74 has been suggested to function as a cytokine and bacterial receptor. CD74 has also been shown to be involved in signalling along with Macrophage migration inhibitory factor (MIF) and CD44 pathways as a survival receptor (Stein *et al.*, 2007; Beswick and Reyes, 2009). CD74 was also demonstrated to be involved in the maturation of B cells through a pathway involving nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) (Stein *et al.*, 2007).

CD74 and the antigen presentation process

The MHC class II molecule is mainly expressed by a limited set of cells called professional antigen presenting cells (APCs), which include cells of the monocyte-macrophage lineage, dendritic cells (DCs) and B-lymphocytes, unlike MHC class I molecules which are ubiquitously expressed on all nucleated cells (Neefjes *et al.*, 2011).

The function of MHC class II is to present antigenic peptides from exogenous origin to a specialized T cell, $CD4^+$ in the presence of invariant chain (CD74). Hence, when CD74 is synthesized, it begins to associate with MHC class II (HLA-DR-α) and MHC class II (HLA-DR-β) within the endoplasmic reticulum (Burton *et al.*, 2004; Stein *et al.*, 2007; Landsverk *et al.*, 2009). The association between these molecules is believed to take place in the rough endoplasmic reticulum through the sequential addition of DR α and β heterodimers to a trimeric core of CD74 molecules in order to from a nine-subunit complex with an equimolar amount of CD74–MHC class II. The resulting complex of CD74 and MHC class II is then gradually transported through Golgi apertures to the late endosomal compartment that is termed the MHC class II compartment (MIIC) either directly or within the plasma membrane. Here, CD74 is digested and cleaved into peptide fragments by endosomal/lysosomal proteases, leaving residual class II-associated Ii peptides (CLIP; amino acids 91-99) in the peptide-binding groove of the MHC class II heterodimer. In order to promote the exchange of CLIP fragments for specific peptides derived from a protein degraded in the endosomal pathway, MHC class II molecules require HLA-DM. By reaching this stage, MHC class II molecules are ready for transporting via the plasma membrane to present their peptides to $CD4^+$ T cells (Burton *et al.*, 2004; Stein *et al.*, 2007; Landsverk *et al.*, 2009; Beswick and Reyes, 2009; Neefjes *et al.*, 2011).

The role of CD74 in cancer

The CD74 expression has been reported in normal tissues and their associated cells such as HLA class II-positive cells, which include number of cell types including macrophages, dendritic cells, monocytes, B cells, activated T cells subsets, cells from thymic epithelium. However, several studies have confirmed that CD74 is highly expressed in inflammatory disorders and several types of tumors (Stein *et al.*, 2007; Beswick and Reyes, 2009). For example, 90% of B-cell cancers and majority of the cell lines derived from these cancers express CD74 in high levels compared to normal tissues (Stein *et al.*, 2007). In particular, CD74 is expressed on different cancer cells, such as myeloma; prostate cancer cells, cancers of the gastrointestinal tract as well as breast cancer (Beswick and Reyes, 2009; Verjans *et al.*, 2009). CD74 expression has also been shown to be correlated positively with gastric cancer stages (Zheng *et al.*, 2012). Recently, CD74 has been classified as a new prognostic factor for patients with malignant pleural mesothelioma (Otterstrom *et al.*, 2014). Moreover, Cheng *et al.* (2015) have also revealed that CD74 has a high potential in treating thyroid carcinoma.

Verjans et al (2009) have shown that breast cancer tissues and breast cancer cell lines overexpressed CD74. Interestingly, it is also reported that CD74 was expressed in tumour cells from 61% of ER–/PR– breast cancer biopsies and from 33% of ER+/PR+ biopsies (Leth-Larsen *et al.*, 2009). Greenwood *et al.* (2011) also revealed that triple negative breast cancer highly expressed signal transducer and activator of transcription (STAT-1) and CD74. Similarly, Tian *et al.* (2012) have shown that CD74 was lower expressed in non-triple negative breast cancer while it is highly expressed on triple negative breast cancer and metastatic lymph nodes. Richard *et al.* (2014) showed that in the absence of estrogen receptors, expression of stromal CD74 is well associated with triple-negative receptor. Recently, according to Yaprak *et al.* (2015) patients who suffer from breast cancer with no CD74 expression had significantly better surgical outcomes than CD74-positive. To emphasize the role of CD74 in tumourigenicity and immunogenicity, the expression of CD74 has been assessed under inflammatory conditions using interferon-gamma and lipopolysaccharide (Greenwood *et al.*, 2011; Zheng *et al.*, 2012). Since then CD74 has been identified as a potential novel target for breast cancer therapies as well as

other types of cancer such as prostate, gastric cancer and thyroid carcinoma (Meyer-Siegler *et al.*, 2004; 2006; Leth-Larsen *et al.*, 2009; Verjans *et al.*, 2009; Tian *et al.*, 2012; Zheng *et al.*, 2012; Richard *et al.*, 2014; Cheng *et al.*, 2015). Gai *et al.* 2018 have shown that the levels of proliferation and invasion were decreased in the CD74 knockdown−HT−1376 cells.

CD74 and IFNg

In terms of proinflammatory cytokines, Möller and Moldenhauer (1999) have shown that the expression of CD74 can be induced using several types of cytokines such as IFN-γ, TNF-α and IL-4. Maubach *et al.* (2007) revealed that CD74 expression was upregulated when hepatic stellate cells (HSCs) were treated with IFN-γ for 30 hr. Martín-Ventura *et al.* (2009) demonstrated that the expression of CD74 increased after IFN-γ treatment in human aortic VSMCs and THP-1 cells. Moldenhauer *et al.* (1999) also showed that the expression of CD74, HLA-DR and HLA-A, B, C increased when colon carcinoma cell lines (HT-29 cells) were incubated with recombinant- IFN-γ (rIFN-γ). Similarly, Burton *et al.* (2010) found that CD 74 expression was up-regulated not only on the surface of cells obtained from acute myeloid leukaemia (AML) but also in the tissues from AML patients when treated with IFN-γ. In the same manner, Greenwood *et al.* (2011) recently demonstrated that the expression of CD74 is upregulated in breast cancer cell lines. Their findings suggested that overexpression of CD74 using IFN-γ treatment increased adhesion of tumour cells (Greenwood *et al.*, 2011). Interferon-gamma (IFN-γ) is a potent proinflammatory cytokine that has many critical roles including; promoting immune responses, immunopathological processes, cell maturation, differentiation, activation, and apoptosis (Pestka *et al.*, 1987; Platt and Hunt, 1998; Dranoff, 2004). It is know that IFN-γ plays a critical role in cancer and cancer progression by controlling apoptosis, cell proliferation, angiogenesis and the expression of MHC class I and II (Sikora and Smedley, 1983; Gooch *et al.*, 2000; Brandacher *et al.*, 2006; Zaidi and Merlino, 2011;). However, IFN-γ has another face that functions against the immune system, and increases the tumourigenicity of tumour cells (Zaidi and Merlino, 2011). There is now emerging evidence that IFN-γ may also be involved at the equilibrium and/or evasion stages, roles that may be more pro-tumourigenic. IFN-γ has been shown to upregulate the suppression of cytotoxic cells (CTL) and NK cell- mediated immune responses, and is central to tumour immune escape (Brody *et al.*, 2009). IFN-γ has also been suggested to enable tumours to escape innate immune system surveillance and influence tumour growth and dissemination by induction of CD74 (Greenwood *et al.*, 2011; Chao *et al.*, 2012).

The role of CD74 in cancer immunomodulation

Research has shown that CD74 plays a significant role in tumour immunosurveillance and cancer immunomodulation. Chao *et al.* (2012) hypothesised that over expressed CD74 might enable tumours to escape the immunosurveillance recognition via evasion of phagocytosis. It is believed that CD74 inhibits phagocytosis via the ligation of expressed signal regulatory protein-α (SIRP-α) by phagocytes resulting in tyrosine activation as well as inhibition of myosin accumulation at the submembrane assembly site of the phagocytic synapse (Tsai and Discher, 2008). So, CD74 functions as a 'don't eat me signal' and a marker of self, as loss of CD74 may lead to phagocytosis of damaged cells (Oldenborg *et al.*, 2000; Blazar *et al.*, 2001; Chao *et al.*, 2012). This process occurs when CD74 on tumour cells binds to SIRP-α on phagocytes leading to promotion of phagocyte inhibition and tumour survival (Chao *et al.*, 2012). In support of this hypothesis, it has been shown that forced expression of CD74 enhances dissemination

and fulminantes death in xenografted mice in a CD74-deficient myeloid leukaemia cell lines (Jaiswal *et al.*, 2009).

CD74 expression by tumour cells has been linked to the process of tumour recognition by T cells and antigen presentation (Beswick and Reyes, 2009). CD74 is thought to be a link molecule between the endogenous and the exogenous antigen presentation pathway as shown recently by Basha and his group (Basha *et al.*, 2012). It has been also shown that CD74 exhibits physical association with HLA-DR promoting re-cycling of HLA-DR into the endosomes. It was proposed that the high level expression of CD74 might prevent the antigen presentation process by blocking the peptide binding cleft rendering tumours less immunogenic. Moreover, it has been demonstrated that upregulation of CD74 in human cancer cells directly influences tumours growth and dissemination suggesting that CD74 may have a role in escaping the equilibrium phase of cancer immuneediting (Chao *et al.*, 2012).

In addition, it has been confirmed recently that blocking CD74 expression on tumour cells by anti-CD74 antibodies may facilitate the elimination of tumour cells by the immune system (Zheng *et al.*, 2012; Otterstrom *et al.*, 2014). It has been suggested that the anti-CD74 antibody eradicates tumour cells through the Fc-dependent mechanism including complement dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC) (Chao *et al.*, 2012). Interestingly, it was found that the anti-CD74 antibody induces cytotoxicity of NK cells against head and neck cancer (Kim *et al.*, 2008). Another suggestion proposed is that blocking CD74 may induce the level of tumour cells apoptosis in vivo and in vitro (Kikuchi *et al.*, 2005; Uno *et al.*, 2007). Anti-CD74 antibody-mediated apoptosis may be involved in the ligation process with thrombospondin ligand activation but is not dependent on the caspase apoptotic pathways (Mateo *et al.*, 2002; Manna and Frazier, 2004). In support of this finding, CD74 has been suggested to be involved in signalling pathways via MIF and CD44 increasing tumour cell survival and inhibition of apoptosis (Tillmann *et al.*, 2013; Yaddanapudi *et al.*, 2013; Richard *et al.*, 2014).

The interaction of CD74 along with MIF and CD44

Several studies have shown that MIF can bind to the extracellular domain of CD74 to promote signalling pathways including inflammatory processes, activation of Extracellular-signal-regulated kinases 1 (ERK1) and Extracellular-signal-regulated kinases 2 (ERK2) members of the family of mitogen-activated protein kinases (MAPKs), cell proliferation, prostaglandin E2 (PGE_2) production, chemokine-mediated signalling and apoptosis (Leng *et al.*, 2003; Shi *et al.*, 2006; Starlets *et al.*, 2006; Bach *et al.*, 2009; Fan *et al.*, 2011; Tillmann *et al.*, 2013). However, the short cytoplasmic tail of CD74 lacks a signal-transducing intracellular domain, although phosphorylation of the serine residues takes place on the P35 variant of CD74 and requires CD44 (Zernecke *et al.*, 2008; Borghese and Clanchy, 2011). The binding of CD44 required MIF mediated cell signaling cascade via Src-tyrosine kinase (Shi *et al.*, 2006) and this also involved chondroitin sulfate, which leads to the formation of receptor complex that activate ERK1 and ERK2 kinases, which further activates number of inflammatory mediators associated events (Borghese and Clanchy, 2011; Naujokas *et al.*, 1993). Interestingly, the extracellular kinases ERK1 and ERK2 remain to be activated for several hours. Therefore, this cell signaling event continues to promote inflammatory process (Mitchell *et al.*, 1999; Lue *et al.*, 2006). Not only have these, Activation of the kinase (Akt) another proinflammatory cell signaling pathway is activated by MIF (Lue *et al.*, 2007). This further activates pro- apoptotic proteins, namely BAD and BAX and the cells acquire signals to withstand apoptosis (Lue *et al.*, 2007). In B-lymphocytes, MIF

induces a signalling cascade that leads to NF-κB activation, proliferation and survival (Matza *et al.*, 2001; Starlets *et al.*, 2006). We have shown recently that CD44 interacts only with p41, the most abundant isoform of CD74 (Al Ssadh *et al.*, 2017). Unpublished data also have confirmed that using siRNA to knockdown CD74 in breast cancer might play a significant role in the apoptosis and proliferation of breast cancer (Al Ssadh Hussain, unpublished data). It has been also shown recently that CD74 expression is associated with better prognosis in Basal-like subtype invasive breast cancer. This association correlates with higher levels of MHCII expression by tumor cells and with a dense TIL response (Wang *et al.*, 2017).

CONCLUSION

The discovery of CD74 and its natural ligand as well as its role in association with its binding partners has led to understand the association of CD74 signaling with the molecular mechanisms present in immunity and cancer. The expression of CD74 in antigen presenting cells is responsible to regulate the process of antigen presentation in presence of MHC class II. However, recent data has shown that CD74 expression may lead to incapacitate the immune system. In addition, various studies including clinical studies revealed that CD74 has a crucial contribution in various diseases and different variety of cancers. Additional researches on CD74 along with its effect on cellular processes, comprising the complex interactions in between CD74 and its binding associates such MIF and CD74, will unquestionably translate into clinical benefit for patients.

Conflict of Interests

The authors declare that they have no conflict of interest.

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دور جزيئات التمايز الخلوي 74 في الأورام السرطانية والتنظيم المناعي للسرطان

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الملخص

تم مؤخرا التعرف على الدور التعبيري لجزيئات التمايز الخلوي (74)، حيث تم إثبات تواجدها في عدة أنواع من الخلايا السرطانية وتم إثبات دورها للتعرف على تكون الأورام السرطانية في جسم الإنسان. وقد أظهرت دراسة حديثة أيضا أنه قد تم التعبير عن تواجد هذه المؤشرات الحيوية بشكل واضح في العديد من الأورام السرطانية مثل سرطان البروستاتا والأورام اللمفاوية نوع بي وسرطان الصدر والمعدة. وذلك من خلال ارتباط الجزء الخارجي للمؤشر الحيوي (74) الموجود على سطح الخلية مع بروتين (إم آي إف) لتبدأ عملية نقل الإشارات بالخلية. بعد هذه الخطوة تبدأ سلسلة من الإشارات الحيوية المتتابعة بالخلية، ولكن الجزء الداخلي للمؤشر الحيوي (74) له القدرة على تثبيط السلسلة التفاعلية مبدئيا بارتباط الذيل القصير للجزء الداخلي للخلية، وهذه العملية تحتاج إلى تواجد المؤشر الحيوي (سي دي 44) وهو بروتين غشائي متعدد الأشكال مسؤول عن تفعيل لإنزيم الكاينيز لتتم عملية الفسفرة. وهذا العملية معقدة وتحتاج إلى الارتباط مع بروتين (إم آي إف) المسؤول عن تنظيم المحفزات (إي آر كي 1 و إي آر كي 2) ومن ثم بدء تنشيط عدة بروتينات مهمة في حالة التهاب الخلية إو إصابتها بعوامل تؤدي بها إلى الموت. فلهذا ركز هذا المقال العلمي على دور جزيئات التمايز الخلوي (74) في مناعية الجسم للأورام وكذلك ترابطها مع المؤشر الحيوي (44) وكذلك مع بروتين (إم آي إف).

الكلمات المفتاحية: الإنتيفيرون غاما، سي دي، عديد السكاريد الشحمي، عرض المستضد للخلايا، مناعية الجسم للأورام.