A REVIEW ARTICLE ON GENE THERAPY OF CD38

Dr. Anil Kumar Yadav* and Prof. She Yuanju

Jingzhou Central Hospital, Jinzhou, Hubei, P.R. CHINA.

ABSTRACT

Gene therapy is an experimental technique that uses genes to treat or prevent disease. CD38 is a transmembrane glycoprotein with both ADP-ribosyl cyclase/cyclic ADP-ribose hydrolase activities. CD38 utilizes NAD(P) as a substrate to produce the second messengers, Nicotinic acid adenine dinucleotide phosphate (NAADP) and Cyclic adenosine diphosphate ribose (cADPR). CD38 has been implicated in several diseases. It can be used as a nobel therapy in this world in several diseases including cancer, diabetes and obesity. So, I had reviewed the role of gene therapy in this article.

Keywords: CD 38, kuromanin, CLL

What is gene therapy?

Gene therapy is an experimental technique that uses genes to treat or prevent disease. In the future, this technique may allow doctors to treat a disorder by inserting a gene into a patient's cells instead of using drugs or surgery. Researchers are testing several approaches to gene therapy, including:

❖ Replacing a mutated gene that causes disease with a healthy copy of the gene.
❖ Inactivating, or "knocking out," a mutated gene that is functioning improperly.
❖ Introducing a new gene into the body to help fight a disease. Although gene therapy is a promising treatment option for a number of diseases(including inherited disorders, some types of cancer, and certain viral infections), the technique remains risky and is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures.

Distribution of CD38:

CD38 is distributed in a number of human and non-human tissues. It has been detected on the

sarcolemma in skeletal and heart muscle, in addition to CD38 localization in the human brain (Mizuguchi et al., 1995; Fernandez et al., 1998). The CD38 molecule has been also found at various locations, including the normal prostatic epithelial cells (Kramer et al., 1995); pancreatic islet cells (Koguma et al., 1994; Mallone et al., 2002); cornea (Sizzano et al., 2007); the kidney; and intra-parenchymatous fibrous septa in the thyroid (Fernandez et al., 1998). Moreover, CD38's presence has been also documented in the inner nuclear envelope, for instance, in the rat hepatocytes, in addition to its localization in the plasma membrane (Khoo and Chang, 2000). 9 CD38 as a cell surface receptor is expressed in cells of hematopoietic origin (Terhorst et al., 1981). However, its expression has been most appropriately termed 'discontinuous' (Jackson and Bell, 1990) since CD38 expression is repeatedly changeable as bone marrow precursors develop into mature elements of the various lineages. For instance, in B cells, CD38 expression is tightly regulated during B cell ontogenesis and is highly present in bone marrow (BM) precursors. However, it is down-regulated in resting normal B cells and then is expressed in terminally differentiated plasma cells (Malavasi et al., 1994). CD38 expression is also changeable in T cells (Deaglio et al., 2001). Furthermore, studies suggest that CD38 is down-modulated during differentiation into immature human monocyte-derived dendritic cells and expressed again upon maturation induced by Lipopolysaccharide (LPS; Fedele et al., 2004). CD38 is also expressed by cells of the innate immune system, including circulating and residential natural killer (NK) cells (Mallone et al., 2001). Collectively, in the immune system, CD38 is expressed by immature hematopoietic cells, down-regulated by mature cells and re-expressed at high levels by activated lymphocytes; T cells, B cells, dendritic cells and NK cells (Funaro et al. 1990). CD38 is also expressed in the BM (Byk et al., 2005), granulocytes (Fujita et al., 2005), circulating monocytes (Zilber et al., 2000), on the surface membrane of erythrocytes and platelets (Zocchi et al., 1993; Ramaschi et al., 1996) and circulating osteoclast precursors (Shalhoub et al., 2000). CD38 has been also detected in lamina propria cells in the gut (Fernandez et al., 1998). Finally, it is worth mentioning that CD157 expression is also involved in most tissues, including the hematopoietic system, like CD38 expression, but the tissue distribution of CD157 is limited compared to CD38 (Ortolan et al., 2002).

CD38 (the type-II & -III glycoprotein) and cyclase crystal structures:

The cyclase crystal structure reveals a homo-dimer; the enzyme is a bean-shaped molecule with most of the β sheets in the carboxyl domain, while the helixes are in the amino domain (Prasad et al., 1996). The two domains are separated by a central cleft, with the active site located in a pocket near the cleft, as shown by crystallography and site-directed mutagenesis (Munshi et al., 1999), with a catalytic residue identified as Glu179. It is interesting to note that for the ADP-ribosyl cyclase, 86 of its 256 amino acid are identical to those in CD38, and an additional 110 amino acids are conservative substitutions (States et al., 1992). However, the structure of human CD38 is more complicated than the cyclase structure (Jackson and Bell, 1990). The structure of CD38 consists of an amino tail of 21 residues, a transmembrane segment of 23 residues and a large carboxyl domain of 256 residues that contains four glycosylation sites

(Jackson and Bell, 1990). The equivalent residue of Glu179 in CD38 is Glu226, which represents the catalytic residue of CD38 (Munshi et al., 2000).

Furthermore, in T cells, the CD38 molecule is also associated with the T-cell receptor (TCR)/CD3 complex (Zubiaur et al., 1999), and it has been shown that CD38 initiated functional signals in a subset of membrane rafts containing CD3 (Zubiaur et al., 2002; Munoz et al., 2003). 16 The observation in immature T cells indicated that CD38 enhances apoptosis when it is crosslinked with a goat anti-mouse antiserum or interacts with CD31 (Tenca et al., 2003). However, it has been shown that following T-cell activation, the final outcome includes cytokine secretion and cell proliferation (Malavasi et al., 2008). In monocytes, CD38 signalling has been shown to be associated with HLA class II and CD9 molecules. The CD38/HLA class II/CD9 complex shares a common pathway of tyrosine kinase activation, and cytokine secretion in human monocytes (Zilber et al., 2005). CD38 expression in human monocytes was found also to be regulated in response to proinflammatory cytokines (Musso et al., 2001). CD38 expression is also known as a marker of the transition of monocytes to dendritic cells (DC) induced by inflammatory processes (Fedele et al., 2004). Furthermore, CD38 mediates important signalling that is involved in dendritic cell migration; the CD38/cADPR signalling pathway is required for the migration of immature dendritic cells to CXC ligand 12 (CXCL12) and of mature dendritic cells to CC ligand 19 (CCL19) and CCL21 (Partida-Sanchez et al., 2004a; 2004b). CD38 is also expressed by resting and activated natural killer (NK) cells; it forms part of a supramolecular complex that includes CD16. Indeed, CD38-CD16 association controls an activation pathway that includes Ca2+ fluxes, increased expression of HLA class II and CD25, tyrosine phosphorylation of cytoplasmic substrates (such as ZAP-70 and ERK), release of cytokines and cytotoxic responses (Mallone et al., 2001). Collectively, the general events that take place after CD38 activation in several cell lineages include calcium (Ca2+) mobilization from cytosolic stores, as well as the triggering of the phosphorylation of a cascade of intracellular substrates, including phosphatidylinositol 3-kinase, leading to the activation of 17nuclear factors (such as the nuclear factor-κB complex), and the secretion of cytokines (Kitanaka et al., 1997; Deaglio et al., 2000).

CD38 as active enzyme:

CD38 is pleiotropic in function (Malavasi et al., 1994); it is considered as the major NADconsuming enzyme in humans (Malavasi et al., 2008). CD38 is capable of catalyzing four major enzymatic reactions: NAD glycohydrolase (NADase), cyclic adenosine diphosphate ribose (cADPR) hydrolase, base-exchange reactions and ADP-ribosyl cyclase activity (Fig. 1.6 A, B). The ADP-ribosyl cyclase activity generates cADPR, and the NADase activity generates adenosine diphosphate ribose (ADPR) directly from NAD (Lee, 2006), while the cADPR hydrolase activity generates ADPR from cADPR (Howard et al., 1993). However, it has been observed that the majority of the NAD (~95%) is converted to ADPR, and only a minor fraction of the total product appears to be cADPR (Howard et al., 1993). Finally,

CD38 can also use NADP+ as a substrate and, in the presence of nicotinic acid (NA), to catalyze the exchange of the nicotinamide (Nam) group of NADP+ with nicotinic acid, producing NAADP and nicotinamide (Lee, 2006). This reaction predominates in acidic conditions, while at neutral and alkaline pH the 18 enzyme mainly catalyzes cyclization of NAD+ (Aarhus et al., 1995). Furthermore, Graeff et al. (2006) documented that CD38 may also catalyse the hydrolysis of NAADP to ADP -ribose 2'-phosphate (ADPRP) at acidic pH. CD38 is also known to metabolize analogs of NAD, such as nicotinamide guanine dinucleotide (NGD) and nicotinamide hypoxanthine dinucleotide (NHD), releasing cyclic compounds (Cyclic guanosine diphosphate ribose (cGDPR) and cyclic inosine diphosphate ribose (IDPR), respectively) with fluorescent properties, but without calciumreleasing activity (Graeff et al., 1994a). cGDPR, unlike cADPR, is a poor substrate for the hydrolase activity of CD38, and thus its measurement provides the basis of a continuous assay of cyclization for distinguishing CD38-like enzymes (with cyclase activity) from classical NADases (Graeff et al., 1994a).

Role of CD38/second messengers in pathophysiological conditions

CD38 and obesity:

Obesity is a major disease, defined as an increase in the body's storage of fat, causing health problems leading to increased mortality (Sorensen et al., 2010). It increases the risk of a number of health conditions, including hypertension, adverse lipid concentrations, and type 2 diabetes (National Institutes of Health, 1998). However, the biochemical explanation for this disease is still unclear. Recently, Barbosa et al. (2007) described a novel and unique role for the enzyme CD38 as a necessary molecule in the biochemical pathway that leads to the development of obesity, as confirmed by CD38 knockout mice studies. CD38 has been implicated in the regulation of a wide variety of signalling pathways in numerous cell types (Galione and Churchill, 2000). For instance, CD38 hydrolase activity (NADase) has a key role in the regulation of intracellular NAD levels and subsequently regulates NAD-dependent deacetylases such as sirtuins; also known as SIRT enzymes (Aksoy et al., 2006). Importantly, SIRT enzymes have been implicated as regulators of energy metabolism, cell life span (longevity) and activation of peroxisome proliferator-activated receptor γ co-activator-1▢ (PGC-1α; Rodgers et al., 2005). The latter is known as a co-activator with pleiotropic function (Knutti and Kralli, 2001). It plays a significant role in energy metabolism and reduces the problems of obesity (Baur et al., 2006), by controlling the function and biogenesis of the mitochondria (Lin et al., 2005). Recent studies have shown that activation of SIRT (by resveratrol) can protect laboratory animals from a high fat diet-induced obesity and its deleterious effects, by increasing levels of PGC1-1α, cellular mitochondrial numbers, and energy expenditure (Lagouge et al., 2006). However, in the case of CD38-deficient mice, one of the possible mechanisms for mice's resistance to diet-induced obesity is mediated via activation of the NAD -dependent deacetylase (SIRT)/PGC1α pathway (Baur et al., 2006). It has been proposed that increasing intracellular levels of NAD following CD38 deficiency will promote activation of the SIRT enzymes. SIRT activation leads to the

activation of PGC1α , which is involved in protection from obesity (Barbosa et al., 2007). Furthermore, several reports have highlighted a crucial role of CD38 as a novel pharmacological target to treat metabolic diseases via NAD+ -dependent pathways. Thus, the manipulation of NAD + metabolism has emerged as a reasonable strategy to improve metabolic syndromes, such as protecting against obesity. More recently, a study by Escande et al. (2013), reported that in vitro and in vivo inhibition of CD38 activity (via quercetin and apigenin) results in elevated cellular NAD levels, decreased overall protein acetylation and improved lipid homeostasis. The crucial role of CD38 deficiency in preventing the development of obesity through activation of SIRT/PGC1α following NAD elevation.In summary, in addition to the knockout of CD38, the inhibition of CD38 activity, and elevation of sirtuin activity were successful mechanisms for preventing the development of obesity, which is part of the NAD manipulation strategy. Another suggested mechanism that might have a beneficial effect is through the activation of one of the NAD biosynthesis pathways to increase NAD levels, which again could activate the SIRT enzymes, consequently leading to an increase in PGG1α activity and reduce the problems of obesity. Successful completion of these proposed studies will lead to a better understanding of obesity and may lead to new therapeutic approaches for this condition.

CD38 and Chronic Lymphocyte Leukaemia (CLL):

Chronic lymphocyte leukaemia (CLL), a B-cell malignancy, is the most frequent leukaemia in the western world, and is characterised by increased lymphocytosis (an increase in the number of lymphocytes) that results from the accumulation of a population of CD5+/CD19+/CD23+mature

B lymphocytes in the peripheral blood, bone marrow (BM) and lymphoid nodes; LN (Rozman and Montserrat, 1995; Van Bockstaele et al., 2009). It is also defined as a disease characterized by a dynamic balance between cells circulating in the blood and cells located in permissive niches in lymphoid organs (Zenz et al., 2010).

There are two subgroups of CLL patients, according to CD38 expression, which correlates with different clinical outcomes (Damle et al., 1999). CLL patients show either an indolent or a progressive course (Caligaris-Cappio and Hamblin, 1999). The two patient subgroups, with CD38+or CD38-CLL, differ clinically in several ways, including overall survival (Ibrahim et al.,2001), time to first treatment (Morabito et al., 2002), bias toward male gender (Damle et al.,1999), number of leukaemic cells with atypical morphology (Morabito et al., 2002), extent and level of adenopathy, lactate dehydrogenase, β-microglobulin levels (Ibrahim et al., 2001; Domingo-Domenech et al., 2002) and absolute lymphocyte counts (Del Poeta et al., 2001).

Hence, CD38+CLL patients have an unfavourable clinical course with a more advanced stage of the disease, poor responsiveness to chemotherapy, and a shorter survival state compared to CD38-CLL

patients (Morabito et al., 2002). Initial studies indicated that CD38 might be useful as a surrogate marker for the absence of mutations in immunoglobulin variable (IgV) genes in CLL patients (Damle et al., 2007). Furthermore, the correlation between CD38 expression levels and cells' susceptibility to apoptosis makes this molecule a valuable prognostic marker and adisease modifier in leukaemia; CLL (Malavasi et al., 2008).

Researchers have confirmed that in combining CD38 with other negative prognostic markers, such as the cytoplasmic kinase zeta1-associated protein of 70 kDa (ZAP-70) and CD49d (Morabito et al., 2009), cytogenetic abnormalities, CD23, b2m, p53 function and cell size (Shanafelt et al., 2004), all together provide complementary prognostic information in CLL. It has been documented that CD38 ligation leads to phosphorylation of the activatory tyrosines within the proliferation marker ZAP-70 (Roos et al., 2008). It has been suggested that CD38 in association with ZAP-70 in CLL may contribute to the signals mediated by the B cell receptor complex (BCR; Chen et al., 2002).

CONCLUSION

Although gene therapy is a promising treatment option for a number of diseases(including inherited disorders, some types of cancer, and certain viral infections), the technique remains risky and is still under study to make sure that it will be safe and effective. Gene therapy is currently only being tested for the treatment of diseases that have no other cures.

REFERENCES

1. Dual role of the CXCL12 polymorphism in patients with chronic lymphocytic leukemia. Butrym A, Gebura K, Iwaszko M, Kuliczkowski K, Bogunia-Kubik K, Mazur G. HLA. 2016 May 13.

2. Metabolism regulates cellular functions of bone marrow-derived cells used for cardiac therapy. Derlet A, Rasper T, Roy Choudhury A, Bothur S, Rieger MA, Namgaladze D, Fischer A, Schürmann C, Brandes RP, Tschulena U, Steppan S, Assmus B, Dimmeler S, Zeiher AM, Seeger FH. Stem Cells. 2016 May 4. doi: 10.1002/stem.2394.

3. CD38+CD8+ and CD38+CD4+ T Cells and IFN Gamma (+874) Polymorphism Are Associated with a Poor Virological Outcome. de Carvalho PG, de Oliveira Rodrigues R, Ribeiro da Silva SF, Ribeiro IF, de Miranda Lucena HB, Martins LR, Rabenhorst SH, de Arruda ÉA, Nagao-Dias AT.Immunol Invest. 2016 May;45(4):312-27.

4. Immune Profiles to Predict Response to Desensitization Therapy in Highly HLA-Sensitized Kidney Transplant Candidates. Yabu JM, Siebert JC, Maecker HT. PLoS One. 2016 Apr 14;11(4):e0153355.

5. Prognostic factors and risk stratification in chronic lymphocytic leukemia. Parikh SA, Shanafelt TD. Semin Oncol. 2016 Apr;43(2):233-40. doi: 10.1053/j.seminoncol.2016.02.009.

6. Pre-clinical evaluation of CD38 chimeric antigen receptor engineered T cells for the treatment of multiple myeloma. Drent E, Groen RW, Noort WA, Themeli M, Lammerts van Bueren JJ, Parren PW, Kuball J,

Sebestyen Z, Yuan H, de Bruijn J, van de Donk NW, Martens AC, Lokhorst HM, Mutis T. Haematologica. 2016 May;101(5):616-25. doi: 10.3324/haematol.2015.137620

7. Longitudinal copy number, whole exome and targeted deep sequencing of 'good risk' IGHV-mutated CLL patients with progressive disease. Rose-Zerilli MJ, Gibson J, Wang J, Tapper W, Davis Z, Parker H, Larrayoz M, McCarthy H, Walewska R, Forster J, Gardiner A, Steele AJ, Chelala C, Ennis S, Collins A, Oakes CC, Oscier DG, Strefford JC. Leukemia. 2016 Jun;30(6):1301-10. doi: 10.1038/leu.2016.10. Epub 2016 Feb 5.

8. Markers of HIV reservoir size and immune activation after treatment in acute HIV infection with and without raltegravir and maraviroc intensification. Ananworanich J, Chomont N, Fletcher JL, Pinyakorn S, Schuetz A, Sereti I, Rerknimitr R, Dewar R, Kroon E, Vandergeeten C, Trichavaroj R, Chomchey N, Chalermchai T, Michael NL, Kim JH, Phanuphak P, Phanuphak N. J Virus Erad. 2015;1(2):116-122

9. Harnessing RNAi-based nanomedicines for therapeutic gene silencing in B-cell malignancies.Weinstein S, Toker IA, Emmanuel R, Ramishetti S, Hazan-Halevy I, Rosenblum D, Goldsmith M, Abraham A, Benjamini O, Bairey O, Raanani P, Nagler A, Lieberman J, Peer D. Proc Natl Acad Sci U S A. 2016 Jan 5;113(1):E16-22. doi: 10.1073/pnas.1519273113.

10. Non-leukemic myeloid sarcoma involving the vulva, vagina, and cervix: a case report and literature review. Yu Y, Qin X, Yan S, Wang W, Sun Y, Zhang M. Onco Targets Ther. 2015 Dec 10;8:3707-13. doi: 10.2147/OTT.S92815.

11. Potential therapeutic targets in plasma cell disorders: A flow cytometry study. Lisenko K, Schönland S, Hegenbart U, Wallenwein K, Braun U, Mai EK, Hillengass J, Raab M, Jauch A, Ho AD, Goldschmidt H, Hundemer M. Cytometry B Clin Cytom. 2015 Dec 15. doi: 10.1002/cyto.b.21351.

12. Establishment and characterization of a novel MYC/BCL2 "double-hit" diffuse large B cell lymphoma cell line, RC. Pham LV, Lu G, Tamayo AT, Chen J, Challagundla P, Jorgensen JL, Medeiros LJ, Ford RJ. J Hematol Oncol. 2015 Oct 29;8:121. doi: 10.1186/s13045-015-0218-1.

13. Expression and Function of NKG2D Is Impaired in CD8+ T Cells of Chronically HIV-1-Infected Patients Without ART. Giuliani E, Vassena L, Desimio MG, Buonomini AR, Malagnino V, Andreoni M, Doria M. J Acquir Immune Defic Syndr. 2015 Dec 1;70(4):347-56.

14. Liquid jet delivery method featuring S100A1 gene therapy in the rodent model following acute myocardial infarction. Fargnoli AS, Katz MG, Williams RD, Kendle AP, Steuerwald N, Bridges CR. Gene Ther. 2016 Feb;23(2):151-7. doi: 10.1038/gt.2015.100. Epub 2015 Oct 13.

15. Re-challenging with anti-CD38 monotherapy in triple-refractory multiple myeloma patients is a feasible and safe approach. Alici E, Chrobok M, Lund J, Ahmadi T, Khan I, Duru AD, Nahi H. Br J Haematol. 2015 Oct 12. doi: 10.1111/bjh.13776.