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Review Article

ROLE OF CD38 IN AGING AND CANCER: A REVIEW

Dr. Devanand Banaita Yadav*[1], Dr. Shahzad M Khan[2], Dr. Ajit Kumar Yadav[3], Dr. Santosh Yadav[4] and Ranju Yadav[5]

[1,2,3]*Clinical School of Medicine, Yangtze University, Jingzhou 434000, Hubei Province, P.R.China*

[1,2]*General Surgery Department, Jingzhou Central Hospital Hubei Province, Jingzhou 434020, P.R. China*

[4]*KIST Medical College and Teaching Hospital Imadol KTM,Nepal.*

ABSTRACT

CD38 is a membrane-bound protein first identified by monoclonal antibody typing of lymphocytes and thus thought of as a lymphocyte-specific antigen. Consistently, its expression in lymphocytes shows stage-related variations and ligation by agonistic antibodies against CD38 can trigger a wide range of responses in various types of blood cells. However, current results show that CD38 is not lymphocyte specific, but is ubiquitously expressed in virtually all tissues. It is present not only on cell surfaces but also in various intracellular organelles, including the nucleus. The unexpected discovery that CD38 is homologous to ADP-ribosyl cyclase has brought in a new perspective on the cellular function of CD38 and ushered in a new field of investigation. So, now it has been established that CD38 is a multi-functional enzyme catalyzing the metabolism of two distinct $Ca2^{+}$messengers, cyclic ADP- ribose (cADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP). The former is a novel cyclic nucleotide that modulates the ryanodine receptor and mobilizes the endoplasmic $Ca2^{+}$ stores.NAADP is structurally distinct from cADPR and targets separate $Ca2^{+}$stores, acidic organelles like lysosomes.

Keywords: CD38, cancer, aging, NAD^{+} (Nicotinamide adenine dinucleotide)

INTRODUCTION

CD38 is a novel multifunctional protein that serves not only as an antigen but also as an enzyme. It catalyzes the metabolism of cyclic ADP-ribose and nicotinic acid adenine dinucleotide phosphate, two structurally and functionally distinct $Ca2^{+}$messengers targeting, respectively, the endoplasmic reticulum and lysosomal $Ca2^{+}$ stores. The protein has recently been crystallized and its three-dimensional structure solved to a resolution of 1.9 Å. The crystal structure of a binary complex reveals critical interactions between residues at the active site and a bound substrate, providing mechanistic insights to its novel multi-functional catalysis. NAD glycohydrolases, a class of enzymes that catalyze hydrolysis of nicotinamide adenine dinucleotide (NAD) into adenosine diphosphate ribose (ADPR) and nicotinamide, are widely distributed in the nature, ranging from bacteria to mammalian systems [1]. Most of eukaryotic NAD glycohydrolase(s) are localized as ecto-enzymes at the outer surface of the cell membrane[2, 3]. Erythrocytes are rich in ecto-NAD glycohydrolase(s), and the surface antigenCD38, a component of erythrocyte membrane[4, 5] has recently evoked considerable interest as the catalyzer of both synthesis of cylic adenosine diphosphoribose (cADPR) and hydrolysis of NAD and cADPR[6-9]. At present, the physiological function of ecto-NAD glycohydrolase(s) is unknown. However,considering the vital importance of NAD metabolism and its close link to the control of signal transduction,cell growth and differentiation in mammalian cells[10-13] alterations of NAD glycohydrolases under pathological conditions appear to be of considerable interest.

Nicotinamide adenine dinucleotide (NAD) is a key cellular metabolite that is involved in cellular energetic. In addition, NAD has recently emerged as a crucial regulator of signaling pathways implicated in multiple physiological conditions[14-25]. The two main signaling roles of NAD include its importance as a substrate for the generation of second messengers such as cyclic-ADP-ribose (cADPR) [14-22] and its role as a substrate and regulator of the NAD dependent deacetylases sirtuins [23-25]. Both these signaling pathways have been shown to be very important in many physiological conditions from egg fertilization all the way to the cellular mechanisms of aging, longevity, and death. In these regards, a great new interest in NAD functions and metabolism has emerged. In fact, we have seen almost asecond discovery of this molecule in recent years [26]. Due to the key role of NAD in cells, it is crucial to characterize the mechanisms that control NAD metabolism. In recent years, we have learned much about the cellular mechanisms of NAD synthesis[25-27].Few studies clearly have shown that the multifunctional enzyme CD38 is a key enzyme involved in the degradation of NAD and appears to control cellular NAD levels [28-30]. The review of this article is to study the role of CD38 in aging and cancer.

Type of cell	CD markers
stem cells	CD34+, CD31-, CD117
all leukocyte groups	CD45+
Granulocyte	CD45+, CD11b, CD15+, CD24+, CD114+, CD182+
Monocyte	CD4, CD45+, CD14+, CD114+, CD11a, CD11b, CD91+,CD16+
T lymphocyte	CD45+, CD3+
T helper cell	CD45+, CD3+, CD4+
T helper cell	CD4, CD25, FOXP3 (a transcription factor)
Cytotoxic T cell	CD45+, CD3+, CD8+
B lymphocyte	CD45+, CD19+, CD20+, CD24+, CD38, CD22
Thrombocyte	CD45+, CD61+
Natural killer cell	CD16+, CD56+, CD3-, CD31, CD30, CD38

Table 1: Types of cells and their CD markers

Biology of human CD38:

Originally defined as a T-cell activation molecule, CD38 expression now does not appear to be dependent on cell lineage or activation[31]. Within the B-cell compartment, CD38 is expressed at high levels by B lineage progenitors in BM and by B lymphocytes in germinal center, in activated tonsils, and by terminally differentiated plasma cells. 24 On the contrary, mature virgin and memory B cells express low levels of the molecule. CD38 also has been found in pancreatic acinar cells, smooth muscle cells, osteoclasts,and in different areas of the brain, although in most of these instances, CD38 is located in the cytosol and/or in the nucleus and not on the cell membrane[31].

The protein encoded by CD38 is a single chain type II transmembrane molecule displaying a canonical molecular weight of ~ 45 kDa. The crystal resolution of the extracellular portion of the molecule showed that the functional CD38 molecule is a dimer,with the central part hosting the catalytic site[32]. The monomer to dimer transition modulates the functions of the molecule. Additional control is rendered by the dynamic localization of CD38 in lipid micro domains of the plasma membrane where the molecule has a tendency to associate with other proteins, forming large supramolecular complexes. CD38-associated molecules in human B cells include the CD19/CD81 complex, the chemokine receptor CXCR4, and adhesion molecules, such as CD49d [31, 33](Figure 1).CD38 is also found in exosomes,[34]membrane vesicles secreted byB cells, and is probably part of an intercellular communication network.

An initial function attributed to CD38 was the regulation of activation/proliferation of human T lymphocytes.[35] Agonistic monoclonal antibodies (mAbs) specific for CD38 induce rapid Ca 2^{+}fluxes and trigger the phosphorylation of a cascade of intracellular substrates, leading to activation of the nuclear factor-ƙB complex.Protracted effects include initiation of genetic programs causing cytokine secretion and proliferation of T lymphocytes.[31] CD31(also known as PECAM-1) is a non-substrate CD38 ligand that can start the signaling cascade and recapitulate the biologic events observed in vitro using surrogate agonistic mAbs[36].

The functional properties of CD38 on human B cells appear to be strictly linked to the stage of maturation. The presence of blocking mAbs in cultures of $CD19^{+}$B-cell precursors on stromal layers markedly suppresses B-cell lymphopoiesis by inducing apoptosis[37]. In addition, in murine systems, CD38 participates in cell selection of transitional B cells[38]. Opposite effects are observed in mature circulating B lymphocytes and tonsillar germinal center B cells, where CD38 ligation is followed by activation, apoptosis inhibition, proliferation, and cytokine secretion. In both instances, the mechanisms are attributed to the activation of an intracellular signaling pathway ruled by CD38 and requiring an association with CD19. The ensuing phosphorylation cascade includes lyn and phosphatidylinositol 3-kinase, among otherkinases[39].

CD38 has a striking similarity (35% amino acid identity) to the enzyme adenosine diphosphate (ADP) ribosylcyclase, which is present in a soluble form in the ovotestis of the mollusk Aplysia californica[40]. This enzyme has the unique characteristic of cyclizing NAD^{+} to generate cyclic ADP ribose (cADPR), a second messenger that releases Ca 2^{+} from internal stores, independently of the IP 3 pathway[41]. Under suitable conditions, a limited amount of cADPR is converted to ADPR. In mammals, CD38 maintained these enzymatic activities and became localized on the cell surface, there by developing into an ecto-enzyme[6](Figure 1). However,evolution preserved the hydrolyzing function, which controls synthesis of ADPR. The human molecule conserves the ability to produce cADPR, even if at very low levels[42]. cADPR is aubiquitous second messenger in eukaryotic cells. Smooth muscle cells of different origins (vascular, bronchial, and uterine)[43-45], 39-41along with epithelial and secretory cells (pancreas, kidney, and hypophysis the most studied)[46], are the best examples. A further enzymatic activity recently attributed to CD38 is the pH-dependent conversion of $NADP^{+}$to $NAADP^{+}$. These products bind different receptors and channels involved in the regulation of Ca 2^{+} and activating critical signaling pathways, leading to muscle contraction (uterus and bronchi) or gland secretion (pancreas and neurohypophysis). These functions were initially described in mice genetically modified to lack or to overexpress CD38[47] and confirmed in human disease models[48].

The family of NAD -consuming enzymes includes 4 classes of enzymes, in which CD38 and the ADP ribosyl transferases are extracellular, whereas (ADP-ribose) polymerases and sirtuins are intracellular. While consuming NAD^{+}as substrate, these enzymes generate nicotinamide, reinforcing the notion that CD38 is

directly involved in maintaining NAD^+ homeostasis[46]. As theNAD^+ /NADH ratio is a direct measure of the energy status of a cell, the NAD^+ dependence of these enzymes directly links cellular energy to metabolism, genomic stability, apoptosis, cell signaling and stress tolerance[46]. Additional novel roles in the control of immunity, inflammatory responses, and in shaping the regulatoryT-cell compartment have now been assigned to extracellular NAD^+[49].

How these varied functional activities can be conducted by a single molecule is yet to be defined. A hypothesis is that they are completely unrelated as enzymatic mutants and enzyme inhibition of CD38 does not impact receptor functions[50, 51] in human B, T, and myeloid cells. An alternative is that the enzymatic functions are regulated through interactions taking place between CD38 and different proteins. The crystal structure of CD38 suggests that CD31 binding regulates accessibility of the substrate to the enzymatic site[32]. If corroborated, one might conclude that the human enzyme is not only limited in function by the availability of the substrate, but it is further finely tuned by the interactions with other non-substrate ligands.

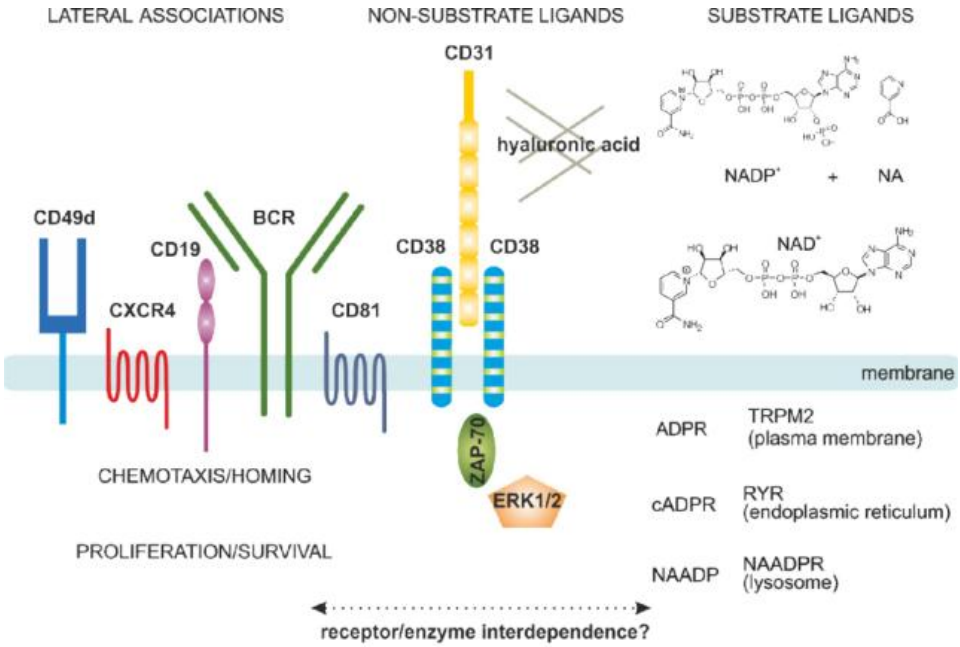


Figure 1: Structural and functional characteristics of the human CD38 molecule. In human B cells, CD38 is expressed as an integral surface membrane molecule, often in a dimeric conformation. As an enzyme, CD38 may interact with the substrate ligands NAD^+ and $NADP^+$, which are converted to cADPR, ADPR, and NAADP, all intracellular Ca^{2+} -mobilizing agents. CD38 also interacts with non-substrate ligands, including CD31 and hyaluronic acid, which regulate cell-cell and cell-matrix contacts. On the plasma membrane, CD38 displays preferential localization in membrane lipid micro domains in close contact with the BCR complex (CD19/CD81) and with molecules regulating homing (CXCR4 and CD49d). CD38 engagement by means of the natural ligand CD31 (or surrogate agonistic mAb) triggers the activation of an intracellular signaling pathway,

which includes ZAP-70 and ERK1/2 as major players. These signals increase chemotaxis as well as proliferation of neoplastic B cells. The interplay between the enzymatic and receptor activities still needs to be determined in the CLL context.

Cd38 Is A Multi-Functional Enzyme:

The first indication that CD38 may been enzyme came from a sequence comparison showing that 86 of the 256 residues of ADP-ribosyl cyclase from Aplysia are identical to CD38[40]. The Aplysia cyclase is the first enzyme that was found to cyclize NAD, a linear molecule, to cADPR, a cyclic product[52].Subsequent studies establish that CD38 indeed catalyzes the cyclization of NAD to produce cADPR[6, 8, 53, 54]. However,unlike the Aplysia cyclase, CD38 cyclizes only a small amount of the substrate,while the majority is hydrolyzed to ADP-ribose instead, providing the first evidence that it is a multifunctional enzyme(Figure 2). Surprisingly, CD38 also uses cADPR, the product, as substrate and catalyzes its hydrolysis to ADP-ribose. This is unexpected because NAD is a linear molecule, structurally distinct from the cyclic and highly compact cADPR, as revealed by X-ray crystallography[55].In fact, CD38 is, so far, the only enzyme ever identified that can hydrolyze cADPR to ADP-ribose.

The functionality of CD38 turns out to extend much farther, and it can use NADP as substrate as well. In the presence of nicotinic acid, it catalyzes the exchange of the nicotinamide group of NADP with nicotinic acid to produce NAADP[56]. Furthermore, most recent results show that CD38 can in fact takeNAADP, the product, as substrate and hydrolyze it to ADP-ribose 2'-phosphate(ADPRP)[57]. Intriguingly, the two reactions involving NAADP occur only at acidic pH.

With the recent finding of the NAAD-Pase activity, the symmetry is thus complete; at neutral or alkaline pH, CD38 catalyzes the synthesis and hydrolysis of cADPR, while at acidic pH, it catalyzes the synthesis and hydrolysis of NAADP instead. The acidic dependence of the NAADP metabolism and its biological function in targeting the acidic Ca 2+ stores in cells[58, 59] may not be asimple coincidence, but, instead, may suggest NAADP functioning as a Ca 2+messenger specifically for the acidic organelles of the endocytic pathwayin cells.

If it were not because of the biological significance of cADPR and NAADP, this multi-functionality of CD38 could just bean irrelevant curiosity of a promiscuous enzyme. Indeed, accumulated evidence over the past decade has firmly established that cADPR and NAADP are Ca 2+messengers active in a wide range of cellular systems that span three biological kingdoms from protist, plant, to animal, including human (reviewed in[18, 60-62]). The cellular functions they regulate are equally widespread and include fertilization[63-65], T-cell activation[66, 67],chemotaxis[68], cell proliferation[69, 70], insulin secretion[71], neurite outgrowth, long-termsynaptic depression, and plant response to stress , just to list a few.

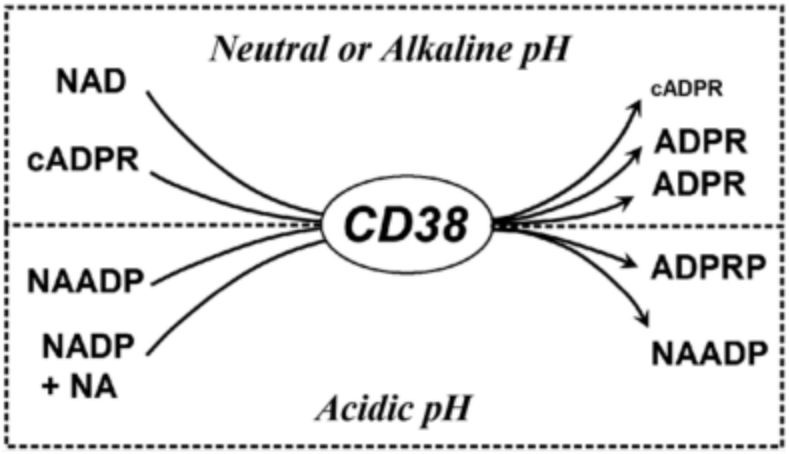
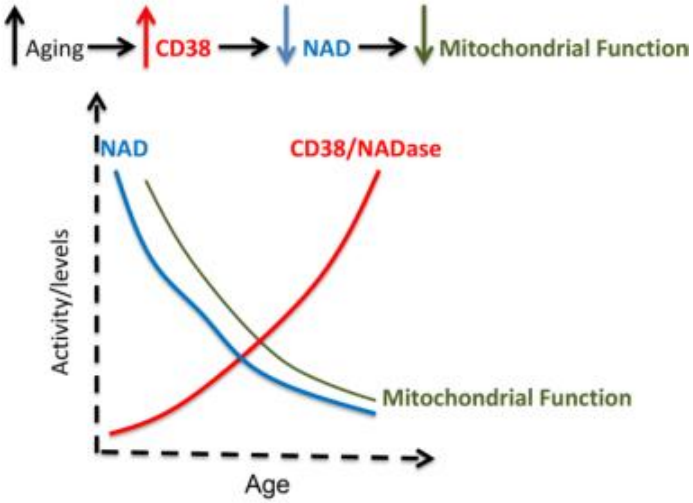


Figure 2: The multiple enzymatic reactions catalyzed by CD38. Abbreviations used: cyclic ADP-ribose, cADPR; ADP-ribose, ADPR; nicotinic acid adenine dinucleotide phosphate, NAADP; nicotinic acid, NA; ADP-ribose-2'-phosphate, ADPRP

Highlights[72]:

- CD38 levels increase in tissues with age and correlate with NAD decline
- NAD and mitochondrial function are preserved in old CD38 Knock-out mice
- CD38 metabolizes NMN in vivo and modulates the response to NAD-replacement therapy



CD38/NADase increases during aging, and causes NAD decline and subsequent mitochondrial dysfunction.

CD38 Plays a Key Role in the Age-Related NAD Decline[72]:

According to some data together show that CD38 protein and mRNA expression increase during aging in multiple tissues, and indicate that this enzyme could play a major role in age-related NAD decline. To determine if these changes in expression were associated with an increase in NAD^+ -degrading activity, So, first measured CD38 NADase activity in tissues from mice at different ages. Consistent with CD38 mRNA and protein expression results, CD38 enzymatic activity also increased during aging in liver, white adipose tissue, spleen, and skeletal muscle. Author also expanded observations and determined that the CD38 NADase activity also increased at least 50% in the ileum,jejunum, and kidney during the aging process. Their control experiments with CD38KO mice confirmed the specificity of the NADase assay for CD38. In fact, they did not detect significant NADase activity in any of the CD38KO tissues tested.

Interestingly, when CD38 activity or protein expression was plotted against NAD^+ decline in aging, an excellent inverse correlation coefficient was observed ($r = -0.95$ and $r = -0.99$,respectively). These results indicated that an increase in CD38 protein expression and activity during aging could be the cause of the age-related NAD^+ decrease. The same was not observed for PARP1. Consistent with adecrease in PARP1 protein expression, levels of PARylated proteins declined in the liver of aged mice. This decrease in PARylation correlated positively with a decrease in both PARP1 protein expression and tissue NAD^+ levels. These findings indicate that the decline in PARylation was potentially a consequence of a decrease in either NAD^+ orPARP1 levels, and do not support a causal role for PARP1 inthe age-related NAD^+ decline.

Demonstration of CD38 is the main enzyme regulating NAD levels, they examined the role of all three NAD^+ degrading enzymes, CD38, PARP1, and SIRT1, in maintaining NAD^+ levels in cells. First, they measured NAD^+ levels in mouse embryonic fibroblasts (MEFs) derived from wild-type (WT),CD38, PARP1, and SIRT1 KO mice. Only CD38KO MEFs showed a significant increase in cellular NAD^+ levels when compared to WT cells. PARP1KO MEFs showed a trend for an increase in NAD^+, but it did not reach statistical significance. They further tested the role of CD38 and PARP1 in regulating NAD^+ levels in vivo, using 1-year-old WT, CD38, and PARP1KO mice. Inagreement with the data in cells, CD38KO had higher NAD^+ levels than both WT and PARP1KO in all tissues tested. Incontrast, although there was a trend for an increase in NAD^+ in this liver and adipose tissue of PARP1KO mice, no statistical significant difference was observed between WT and these mice. To directly test the hypothesis that CD38 was responsible for the age-related NAD decline, they measured NAD levels in tissues from WT and CD38KO mice at various ages.Consistent with their hypothesis,they observed that although NAD^+ levels declined significantly during chronological aging in all WT tissues, they were stable in CD38KO mice. In sharp contrast, in CD38KO mice NAD levels remained constant at all ages. In the liver, in particular,neither NAD^+ nor NADH levels significantly decline in CD38KO mice. These results were observed using both the cycling and the UPLC-mass spectroscopy assays and

demonstrate for the first time that CD38 has a major role in regulating NAD levels during the aging process.

CD38 Regulates Mitochondrial Function in Mammalian:

Tissues during Aging Mitochondrial function decline is a hallmark of aging[73], and cellular NAD^+ decline has been implicated as a potential cause of this age-related mitochondrial dysfunction. Here we investigated the role of CD38 in the development of mitochondrial dysfunction during the aging process in liver tissue. First, we observed that there spiration-driving ATP synthesis decreases almost 70% in WT liver mitochondria (LM) during aging (Figure 3A), and this decrease correlated positively with the age-related decreasein NAD^+ levels. In agreement with the role of CD38 in the age-related NAD^+ decrease, the decline in mitochondrial function was forestalled in CD38KO mice.

Oxygen consumption rates in LM were at least 2.5 times higher in all respiratory states in 1-year-old CD38KO mice compared to WT mice, irrespective of the substrate used. Similar results were also observed in mitochondria isolated from spleen of 1-year-old mice or in LM from 2-year old mice submitted to normal or high-fat diet. These results, together with the higher mitochondrial membrane potential observed in 1-year-old CD38KO mice, confirm the increased mitochondrial activity in these animals. Higher levels of NAD^+ and NAD^+ /NADH ratio were also detected in the mitochondria of 1-year-old CD38KO mice. Thus, we propose that chronic increases I cellular NAD levels in CD38KO mice also lead to increases in NAD in cellular compartments such as mitochondria.

To further explore the role of CD38 in mitochondrial function,we measured the expression of mtDNA and of the mRNA of mitochondrial enzymes. mtDNA copy number was not significantly different between 1-year-old WT and CD38KO suggesting that the number of mitochondria was not altered in liver of CD38KO mice. This observation was further supported by the relative expression of genes involved in mitochondrial biogenesis such as PPAR-g, PGC1a, and NRF1 in liver from 1-year-old WT and CD38KO mice. Interestingly, we found that mRNA levels of Pdha1 and PDK2 that are involved in pyruvate entrance into mitochondria were decreased in CD38KO mice. We also found a decrease in mRNA expression levels in glycolytic/pentose pathway enzymes and small solute carriers in LM of 1-year-old CD38KO mice compared to WTmice. These changes may be compensatory to an increase in mitochondrial oxidative capacity and mitochondrial NAD levels. Our results in animals indicate that there is an increase in oxygen consumption in CD38KO mice, which is related to an increase in mitochondrial NAD, and not mitochondrial biogenesis.

Types of cells	Indicate
Increased CD8+ CD38+	Poor prognostic factor for HIV+
Median fluorescence intensity of CD38 expression on memory (CD45RO) CD38 T cells	Correlates with HIV RNA viral load
Autoimmune reactions against CD38	Is associated with newly diagnosed type-1 diabetes

Table 2

DISCUSSION

The correlation between NAD glycohydrolase activities and degrees of anemia has raised the question whether the CD38-associated enzyme activities (and/or receptorial activities[74]) have a relationship to erythropoesis and, respectively, erythrocyte maturation. Work with different cell lines of hematopoietic origin, indeed, attests to differentiation-dependent expression of CD38 with elevation of NAD glycohydrolase and ADP-ribosyl cyclase activities[75, 76]. The expression of CD38 may have a relationship to the erythrocyte ontogeny and be involved in the survival of erythroblasts from apoptosis in erythropoetic process [74, 77].CD38 may be as well a marker of the intensity of red blood cell turnover and reflect the proportion of young erythrocytes in peripheral blood. The age-dependent fractionation of erythrocytes by centrifugation in percoll gradients failed, however, in our case to provide any conclusive results in favor of such a shift,since distribution of erythrocyte subsets corresponding to different age groups revealed similar profiles in both cancer cases as well as controls. On the other hand, erythrocyte aging appeared to result in decline of CD38-associated enzyme activities.A higher content of a 45-kDa protein with anti-CD38 reactivity was found in erythrocyte ghost protein fraction from cancer patients. This finding provides a plausible explanation for elevated CD38-associated enzyme activities in cancer patients,although post synthetic modifications may additionally give rise to modulation of this activities[78].Both high CEA values as well as anemia are regarded as indicators of tumor progression. It is of importance to note in this context that CD38 expression has been recently found to be prognostic marker in chronic lympho proliferative leukemia[79].

One of the current hypotheses to explain the age-related NAD decline is that this phenomenon could be mediated by accumulation of DNA damage and activation of PARP1 during aging[80, 81].However, there is no consensus about the role of PARPs in the aging process, and the concept to fade leterious increase in PARP activity during aging is controversial. In fact, it has been previously observed that levels of PARPs may either decrease or increase with aging[82-85]. Furthermore, based on the disposable soma evolutionary aging hypothesis, it is expected that the aging organism would present limited repair mechanisms and not necessarily an increase in damage inputs or repair machinery[86]. In fact, in the disposable soma theory, it has been proposed that to optimize energy use, biological systems may invest most of their energy in growth

and development and little in damage control and repair. In support of this idea, some data indicate that PARP1 levels actually decrease in all mouse tissues tested during the aging process. Thus, other NAD-degrading mechanisms besides PARP1 activation is responsible for the age-related NAD^+decline. Current studies further provide evidence that an increase in CD38 in aging mice correlates with the development of mitochondrial dysfunction. The effects of CD38 on mitochondrial function may be mediated, at least in part, by modulation of the availability of NAD^+ as a substrate to mitochondrial enzymes,including SIRT3. However, since CD38 regulates both global cellular and mitochondrial NAD levels, we cannot exclude the possibility that the effect of CD38 may be mediated by interference in many of the other cellular NAD^+ -dependent processes,including oxy-reduction reactions, signaling, and epigenetic.At this point, it is not clear if the biological effects of CD38 in NAD^+ metabolism are exclusively mediated by its extracellular or intracellular NADase activity. The fact that CD38 metabolizes not only NAD but also NMN may indicate that CD38 could at least in part decrease the availability of extracellular and intracellular NAD precursors to cells during the aging process.

CONCLUSION

Thus, it is interest to note that CD38-ligation with specific agonistic monoclonal antibody and interaction with its counter-receptor CD38, results in release of IL-1b, IL-6 and IL-10 cytokines in resting human monocytes. The secretion of these cytokines displays an enhancement upon induction of surface CD38-receptors by treatment of monocytes with IFNg. Thus, CD38 is implicated to play a pivotal role in the cross-talk between cancer cells and immune system and respectively in a positively feed-backed process leading to secretion of cytokines. There is strong evidence that CD38 is a key enzyme involved in the age-related NAD^+ decline. The recent development of potent and specific CD38 inhibitors, together with the novel findings high lighting the role of NAD^+ -replacement therapy and CD38 inage-related diseases such as hearing loss and Alzheimer's indicate that CD38 inhibition combined with NAD precursors may serve as a potential therapy for metabolic dysfunction and age-related diseases.

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