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CD200: a putative therapeutic target in cancer

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Abstract

CD200 was recently described as a new prognosis factor in multiple myeloma and acute myeloid leukemia. CD200 is a membrane glycoprotein that imparts an immunoregulatory signal through CD200R, leading to the suppression of T-cell-mediated immune responses. We investigated the expression of CD200 in cancer using publicly available gene expression data. *CD200* gene expression in normal or malignant human tissues or cell lines was obtained from the OncoPrint Cancer Microarray database, Amazonia database and the ITTACA database. We found significant overexpression of *CD200* in renal carcinoma, head and neck carcinoma, testicular cancer, malignant mesothelioma, colon carcinoma, MGUS/smoldering myeloma, and in chronic lymphocytic leukemia compared to their normal cells or their tissue counterparts. Moreover, we show that *CD200* expression is associated with tumor progression in various cancers. Taken together, these data suggest that CD200 is a potential therapeutic target and prognostic factor for a large array of malignancies.

Introduction

Tumor cells may escape from immune control by producing immunosuppressive molecules, lacking T cell costimulatory molecules or downregulating the presentation of tumor peptides through HLA complexes. Two recent studies have shown that the *CD200* gene is overexpressed in malignant plasma cells and in acute myeloid leukemia cells in association with bad prognoses [1].

CD200 is type 1a transmembrane protein, related to the B7 family of costimulatory receptors, with two extracellular domains, a single transmembrane region, and a cytoplasmic tail with no known signaling motif. CD200 is expressed by thymocytes, activated T cells, B cells, dendritic cells, endothelial cells and neurons [2]. The expression of the receptor for CD200 (*CD200R1*) is restricted to monocyte/macrophage lineage and certain populations of T cells [3]. Three other genes, closely related to *CD200R1* and termed *CD200R2-4*, have been identified, but the function of the encoded proteins, in particular their ability to bind CD200, is not known [4]. Interaction of CD200 with its receptor imparts an immunosuppressive signal leading to inhibition of macrophages [5; 6], induction of regulatory T cells [7], switching of cytokine profiles from Th1 to Th2 [8] and inhibition of tumor-specific T cell immunity. In a murine model [9], an increase in *CD200* expression in both hepatic and splenic dendritic cells (DCs) results in increased survival of renal allografts following portal vein immunization with alloantigen. This tolerigenic effect was reversed by a monoclonal antibody to CD200 [10]. CD200-deficient mice have a compromised capacity to down-regulate the activation of antigen presenting cells. This results in chronic central nervous system inflammation, which causes an exaggerated inflammatory response to trauma and an increased susceptibility to develop both experimental autoimmune encephalitis and collagen-induced arthritis

[5]. More recently, Gorczynski *et al.* demonstrated that anti-CD200R (2-4) monoclonal antibodies (MoAb) promote the development of DCs and have the capacity to induce regulatory T cells (Treg) and directly augment the production of Treg in the thymus [7]. CD200 is also involved in the immunosuppression in B cell neoplasias. B-cell chronic lymphocytic leukemia cells express CD200, which leads to the inhibition of the Th1 response in mixed lymphocyte reactions [11]. More recently, Kretz-Rommel *et al.* demonstrated that CD200 expression in Burkitt's lymphoma cell lines prevents the rejection of tumor cells by human PBMC in a NOD/SCID hu-mouse model [12].

These data demonstrate that CD200 is a potent immunosuppressor in autoimmune, transplantation and tumor settings. Therefore, we looked for *CD200* expression in various cancers compared to their normal tissue or cell counterparts and in association with staging.

Materials and methods

Databases

CD200 gene expression in normal or malignant human tissues or cell lines was obtained from the Oncomine Cancer Microarray database (<http://www.oncomine.org>) [13], Amazonia database (<http://amazonia.montp.inserm.fr/>) [14] and the ITTACA database (Integrated Tumor Transcriptome Array and Clinical data Analysis) developed by the Institute Curie Bioinformatics group and the Institute Curie, CNRS UMR144 [15] (<http://bioinfo-out.curie.fr/ittaca/>). Only gene expression data obtained from a single study using the same methodology were compared. All data were log transformed, median centred per array, and the standard deviation was normalized to one per array [16].

Statistical analysis

Statistical comparisons were done with Mann-Whitney or Student t-tests.

Results and Discussion

CD200 expression was analyzed in normal tissues using Affymetrix published data from Su *et al* [17]. The majority of tissues were negative for *CD200* expression. *CD200* was expressed at low levels by CD34 hematopoietic progenitors, tonsil, DC, cardiac myocytes, lymph node, peripheral B cells and the uterus. The brain and placenta were highly positive for *CD200* expression (Supplementary figure S1). We also investigated the expression of CD200 in normal tissues using non Affymetrix published data from Shyamsundar *et al* [18]. *CD200* is highly expressed in brain as observed previously but also in the fallopian tube and thyroid. Bladder, lymph node, thymus, tonsil, uterus and ovary were also positive for *CD200* expression (Supplementary figure S1).

We investigated the expression of CD200 in cancer using publicly available gene expression data. CD200 expression by microarray analysis was already validated in MM and in acute myeloid leukemia by real time RT-PCR and flow cytometry, and the data sets were highly correlative [1; 19]. We found significant overexpression of *CD200* in renal carcinomas compared to normal kidneys [20]; $P = 1.9E-6$), in head and neck carcinomas compared to normal oral mucosa [21]; $P = 1.8E-7$), in testicular cancer compared to normal testes [22]; $P = 4E-12$ and [23]; $P = 1.9E-5$), in malignant mesothelioma compared to normal pleura [24]; $P = .002$), in colon carcinoma compared to normal colonic epithelia [25]; $P = 0.02$) and in smoldering myeloma compared to normal plasma cells [26]; $P = 1.8E-4$) confirming our recent study [19] (Figure 1). We found significant overexpression of *CD200* in chronic

lymphocytic leukemia compared to normal B cells [27] ; $P = 4.8E-17$) (Figure 1). In contrast, the expression of *CD200* in Burkitt lymphoma, diffuse large B cell lymphoma and follicular lymphoma was not different from that in normal B cells.

Recently, Tonks A *et al.*[1] and our group [19] demonstrated that *CD200* expression is associated with a poor prognosis in AML and MM respectively. We searched to identify if *CD200* expression could be associated with tumor progression in other cancers (Figure 2). Indeed, we found that *CD200* is significantly overexpressed in invasive bladder carcinoma compared to superficial bladder carcinoma in two independent studies ($P = 9.1E-6$ and $P = 0.001$) [28; 29]. *CD200* was also overexpressed in patients presenting advanced lung cancer stages (stages II, III and IV) compared to stage I [30]. Chronic myelogenous leukemia is grouped into several phases: the chronic phase, the accelerated phase and the blast crisis phase consistent with the progression of the disease. *CD200* appears to be significantly overexpressed in CML cells in the accelerated phase compared to the chronic phase ($P = 0.03$) and in blast crisis compared to the accelerated phase ($P = 0.04$) and chronic phase ($P = 3.5E-7$) [31]. In CML, *CD200* expression is upregulated during disease progression. In breast cancer, *CD200* is overexpressed in patients presenting metastases at 5 years compared to patients without metastases ($P = 0.009$) [32] and in relapsing patients compared to patients without progression ($P = 0.004$) [33]. Metastatic melanoma showed an overexpression of *CD200* compared to primary melanomas and normal melanocytes ($P = 0.01$) [34]. Prostate cancer progression was also characterized by an enhanced expression of *CD200* ($P = 0.01$) [35].

The analysis reported here demonstrates that *CD200* mRNA is overexpressed in at least 8 cancers compared to their normal counterparts, and within a given tumor

category, is associated with a bad prognosis. A recent study reported the co-expression of CD200 with cancer stem cell markers found on prostate, breast, brain and colon cancers [36]. Given the immunosuppressive role of CD200, overexpression of CD200 in cancer tissues may facilitate an escape from the immune response and provide a mechanism whereby cancer stem cells are able to avoid detection by the immune system and remain as residual disease. As indicated above, antibodies to CD200 can abrogate its immunosuppressive effect, and in particular, restore tumor immune control in murine models. Thus, the targeting of CD200 may be promising in a large number of cancers. CD200 emerges as a candidate target in a very wide panel of malignancies.

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Figure legends

Figure 1: CD200 expression in various cancers.

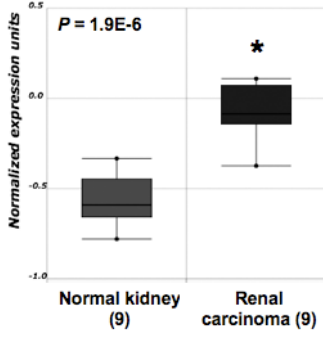
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Figure 2: Association between CD200 expression and progression in various cancers.

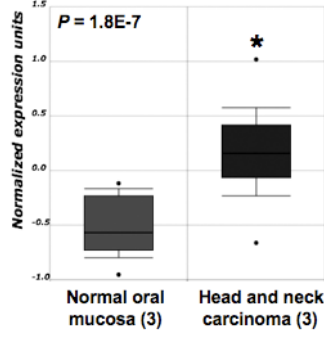
CD200 gene expression in superficial bladder carcinoma, invasive bladder carcinoma [29], lung cancer [30], chronic myelogenous leukemia [31], breast cancer [32; 33], primary melanoma, metastatic melanoma [34], prostatic intraepithelial neoplasia and prostate carcinoma [35]. Data sets in a single panel were from the same study. GEP data are log transformed and normalized as previously described [16].

Figure 1

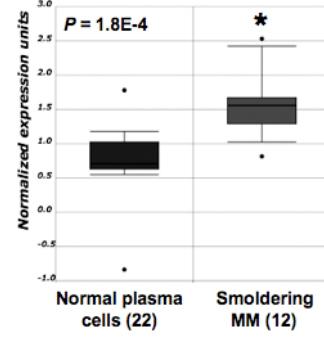
CD200 expression



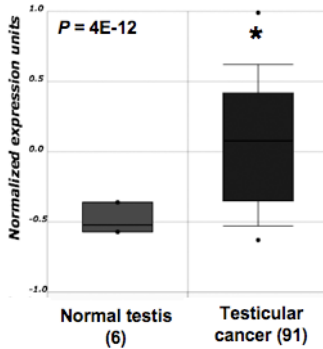
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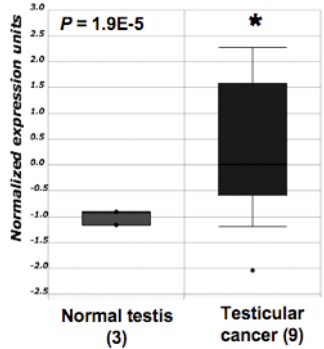
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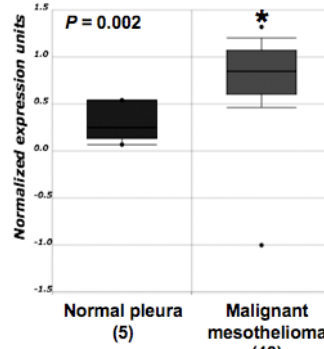
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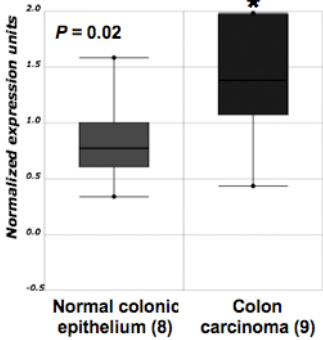


Skotheim et al. Cancer Res 2005

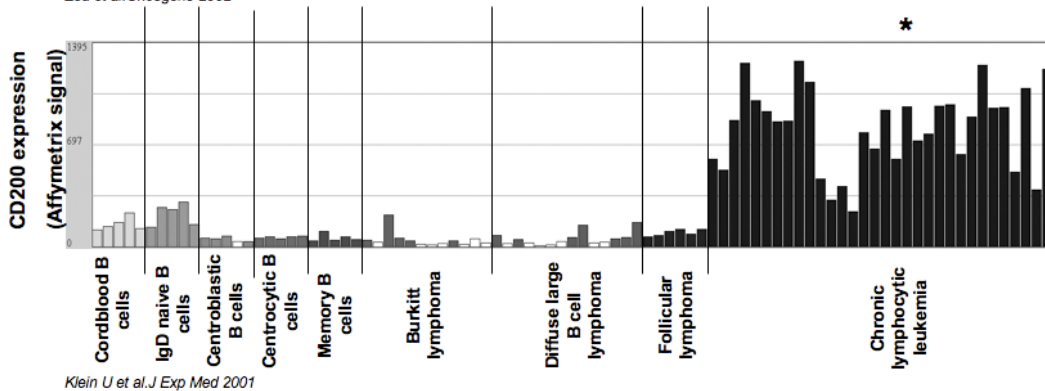


Gordon et al. Am J Pathol 2005

CD200 expression



Zou et al. Oncogene 2002



Klein U et al. J Exp Med 2001

CD200 expression

