

Enhanced T-cell activation and T-cell-dependent IL-2 production by CD83⁺, CD25^{high}, CD43^{high} human monocyte-derived dendritic cells

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Abstract

Although standardized protocols are widely used for the generation of monocyte-derived immunostimulatory dendritic cells (DC_{ims}), the inducibility of Th1 cells by DC_{ims} may considerably differ. As a measure for the quality of DC_{ims} generated from an individual donor at a certain time point, CD83 is used in combination with HLA-DR and CD86 to assess DC maturation. When phenotypically analyzing DC_{ims}, we identified a subpopulation (~60%) of CD83⁺, CD86⁺, and HLA-DR⁺ DC_{ims} that co-expressed CD25. DC within a given DC_{ims} preparation identified by lower expression of CD83 and by selective expression of CD14, however, did not co-express CD25. In order to establish CD25 as an additional maturation marker of DC_{ims}, we studied the DC phenotype of these cells as well as the DC-dependent T-cell proliferation and T-cell cytokine production profile after co-incubation with sorted CD25^{high} and CD25^{low} subpopulations of CD83⁺, HLA-DR⁺, CD86⁺ DC_{ims}. CD25^{high} DC_{ims} showed significant up-regulation of the DC activation molecule CD43 and induced increased levels of IL-2 secretion in allogeneic T-cells (170.7 ± 86.7 pg/mL) as compared to T-cells coincubated with CD25^{low} DC_{ims} (86.6 ± 37.6 pg/mL) [$p = 0.0224$]. This was reflected by a significantly lower T-cell stimulatory capacity of CD25^{low} DC_{ims} (84.0% of CD25^{high} DC_{ims}; 1:10 ratio; $p = 0.014$) whereas the T-cell stimulatory capacity of CD25^{low} DC_{ims} was much higher when compared to IL-10 induced regulatory DC (55.3% of CD25^{high} DC_{ims}; 1:10 ratio). With regard to cancer vaccination protocols, we propose to use CD25 and CD43 as additional markers for DC quality control, assessment of maturational status, and positive selection. © 2006 Elsevier Ltd. All rights reserved.

Keywords: Dendritic cells; CD25; Cancer vaccination; Proinflammatory immune response

1. Introduction

In vaccine development, DC are a promising adjuvant due to their unique properties as antigen presenting cells and their ability to prime naïve T-cells. Increasing evidence suggests that the maturation stage of DC critically influences the outcome of the immune response. The majority of DC for clinically applicable DC-based vaccination strategies are generated from monocytes (moDC) using a cocktail of cytokines comprising TNF- α , IL-

1 β , IL-6 and PGE₂ as a gold standard (Jeras et al., 2005). Since human autologous serum is added during the culture, plasma components and acute phase proteins that reflect the inflammatory condition of the donor could impair maturation of fully competent DC (Tobiasova-Czetoova et al., 2005). Plasma levels of steroid hormones that show daily (glucocorticoids) or menstrual cycle (estradiol) variations could interfere with cytokine-induced DC maturation (Bengtsson et al., 2004). Disease-related alterations in cytokine-driven maturation of moDC such as allergies, viral infection or tumors further contribute to insufficient maturation of moDC (Jiang et al., 2005; Katsenelson et al., 2001; Metharom et al., 2006). In addition, alcohol and tobacco consumption further contribute to the suppression of moDC maturation (Barrett et al., 1991).

In order to successfully employ DC preparations as nature's own adjuvant especially in cancer immunotherapy, it is indispensable to optimize the selection of fully mature moDC.

Abbreviations: DC_{ims}, immunostimulatory myeloid dendritic cells; DC_{reg}, regulatory dendritic cells

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Adverse effects of heterogeneous preparations of partially immature DC, i.e. induction of tumor tolerance instead of tumor immunity potentially worsening the patients' condition, must be avoided. This could be achieved by the identification and routine application of suitable DC maturation markers. Current maturation markers of DC include CD83, CD80, CD86, HLA-DR and CCR7 (Figdor et al., 2004). However, CD83 shedding and degradation in DC has been associated with complete inhibition of DC – T-cell interactions leading to antigen-nonspecific energy (Kotzor et al., 2004). The use of CD86 and HLA-DR as maturation markers has been hampered by the fact that both markers are also up-regulated in glucocorticoid-treated immunoregulatory DC (Duperrier et al., 2005). Thus, additional maturation markers are desirable to guarantee competent selection of efficiently immunostimulatory DC for optimal DC immunotherapy.

When phenotypically analyzing different subsets of immunostimulatory dendritic cells (DC_{ims}) and regulatory DC (IL10-treated DC [DC-IL-10]), we detected a considerable percentage of CD25+ cells among CD83– DC-IL-10 and a lower number of CD25+ cells among CD83+ DC_{ims} (Velten et al., 2004). Other studies detected CD25 expression on various DC types such as mouse splenic (Crowley et al., 1989), thymic (Ardavin and Shortman, 1992), and lung DC (Pollard and Lipscomb, 1990), as well as on epidermal Langerhans cells and on human blood DC (Freudenthal and Steinman, 1990). Despite these repeated observations, human CD25+ DC has not been further characterized. This may be due to the fact that results derived from mice indicate that CD25 is non-functional as the IL-2 receptor in DC since the IL-2 receptor β -chain is not expressed (Kronin et al., 1998). Here, we sought to analyze DC_{ims} subsets that differentially express CD25 using

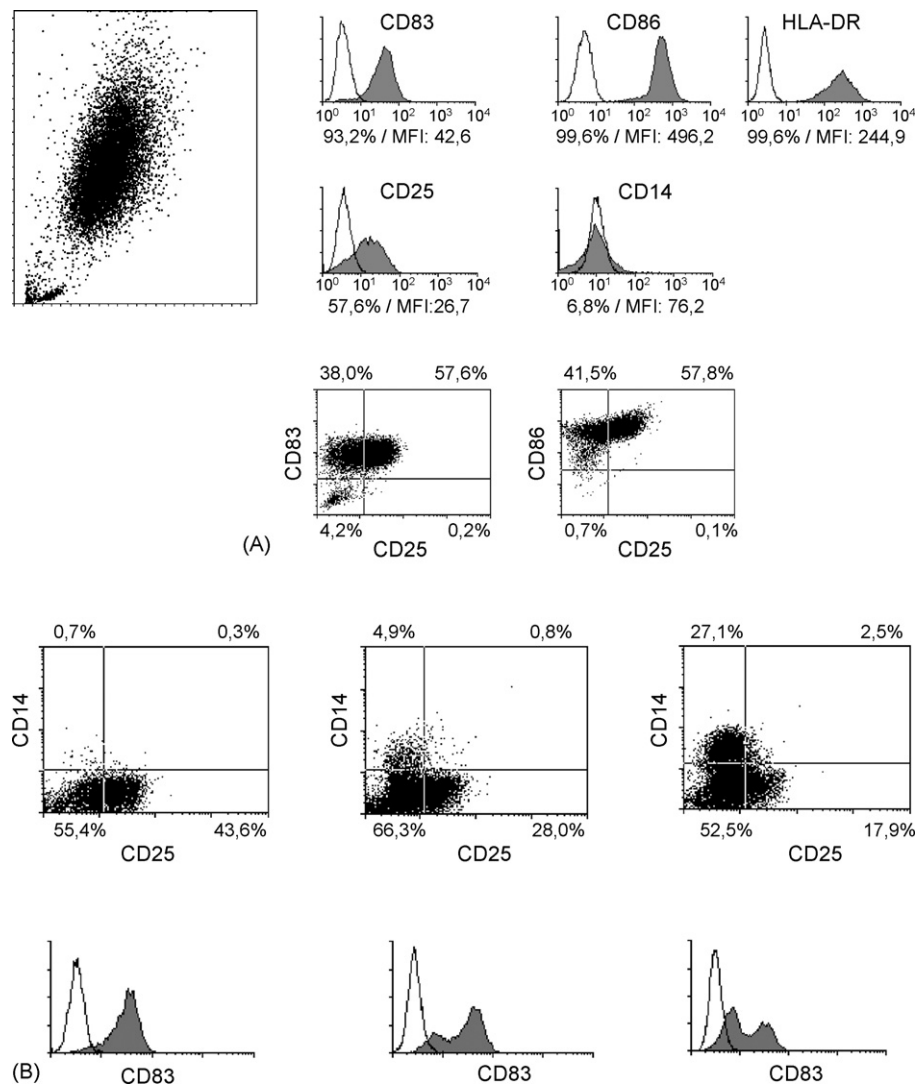


Fig. 1. Phenotypic analysis of immunostimulatory dendritic cells (DC_{ims}). (A) Day 9 DC_{ims} were stained with combinations of monoclonal antibodies against standard maturation markers (CD83, CD86, HLA-DR), CD25, and CD14 as a marker for monocytes and tolerogenic DC_{reg}. (B) CD25, CD14, and CD83 staining of three day 9 DC preparations showing different stages of DC_{ims} maturation. The surface markers used are represented by filled histograms. Isotypic-matched antibodies were used as controls (empty histograms). FACS analysis performed on cells generated from six to seven donors.

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