The plasticity and potential of leukemia cell lines to differentiate into dendritic cells (Review)

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Abstract. Dendritic cells (DCs) are potent antigen-presenting cells that orchestrate the innate and adaptive immune systems to induce immunity. DCs are significant in maintaining immune tolerance towards self-antigens, organ transplantation and allergic responses. DCs are powerful adjuvants for eliciting T-cell immunity and are therefore considered primary targets for inducing immune responses in the prevention and treatment of infectious diseases and cancer. DCs have been increasingly applied in the immunotherapy of cancer worldwide during the last decade; however, a number of the highly specialized biological characteristics of DCs remain to be elucidated. Previous studies of human DCs have been constrained by certain difficulties, therefore the majority of studies have been carried out using *in vitro* model systems. Suitable cell lines with dendritic-like properties may provide valuable tools for the study of DC physiology and pathology. In the current review, various human DC line differentiation models are discussed. Certain cell lines provide valuable tools for studying the specific aspects of DC biology, despite variations in cell biological and immunological features when compared with primary DCs.

Contents

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1. Introduction

Dendritic cells (DCs) are hematopoietic cells that belong to the antigen-presenting cell (APC) family, which also includes B cells and macrophages. They are responsible for the induction of cellular immune responses, by recognizing, acquiring, processing and presenting antigens to naïve, resting T cells for the induction of an antigen-specific immune response. Of all the antigen presenting cells, DCs are the most effective inducers of T-cell-based immunity (1). DCs originate from myeloid precursors that, during their development, progress from the blood into the peripheral tissues. DCs reside in the peripheral tissues in an immature state (iDCs) equipped with specialized receptors, including toll-like receptors, C-type lectins, the cytoplasmic NOD/NALP family, RIG-I/DDX58 and MDA5/IFIH1 molecules and Fc receptors, where they capture and process antigens for presentation in the context of MHC molecules (2). iDCs undergo a maturation process in response to pathogens, antigens and/or pro-inflammatory signals, during which they acquire the morphological, phenotypical and functional characteristics of mature DCs (mDCs). During maturation, DCs upregulate the major histocompatibility complex (MHC) and remodel their surfaces, typically expressing numerous membrane-associated co-stimulatory molecules (including members of the B7, TNF and notch families) (3). Subsequently, mDCs progress into the secondary lymphoid tissues, where they present the processed antigens to naïve T cells to generate effector T cells. Since DCs are so well equipped for initiating adaptive immune responses, they are considered to be prime targets for modulating immune responses against cancer. In the overt absence of maturation stimuli, steady state DCs induce tolerance when they capture self and environmental antigens (4).

Worldwide, research is being conducted to explore the therapeutic application of DCs; however, numerous aspects of DC-biology remain poorly understood. Studies of human DCs have been constrained by various factors. Firstly, differentiated DCs are predominantly located in the tissue rather than the blood, making isolation and analysis more difficult. Although DCs are isolated from either the spleen (5) or blood (6,7), their low and varying levels often hamper studies by making it difficult to generate large amounts of immunostimulatory DCs. Second, the life span of the culture

is limited since DCs are terminally differentiated and cannot divide. Although larger numbers of DCs may be derived by the *in vitro* differentiation of bone marrow stem cells (8), peripheral blood mononuclear cells (9) or monocytes (10), the isolation of these DC-precursors is laborintensive and the generation of typical DCs is dependent on the differentiative stage of the primary culture. The subsequent differentiation is also time consuming. Third, these cultures do not sustain DC production for long periods of time and do not allow the identification or study of the intermediate stages as the majority of cytokine-supplemented cultures drive progenitors quickly to mDCs. Moreover, the current methods of preparation *ex vivo* or from primary cell culture are not only laborious, but suffer from the inherent difficulties of reproducibility associated with the study of primary human material. Finally, experiments using these primary cells are often complicated by donor-donor variations in cytokine expression levels, cell surface molecule expression levels and the ability to stimulate T cells. Hence, there is a significant requirement for model cell lines to aid in the understanding of the developmental origins of DCs and the aspects that are induced to undergo maturation in response to pathogens or cytokine stimulation. It has been described that the 'dendritic-like' cells are established from the leukemia-derived cell lines that are capable of differentiating into functional DCs (37). This creates possibilities for the development of highly reproducible DCs and providing *in vitro* model systems for in-depth studies concerning DC physiology.

This review outlines a number of human DC line differentiation models, various leukemia cell lines, multiple differentiation potentials and the plasticity to differentiate into DCs. The evidence suggests that various leukemia cell lines retain the potential for terminal differentiation into diverse peripheral mature cell types, even DCs.

2. HL-60 cells

The HL-60 cell line, derived from a patient with acute promyelocytic leukemia (APL), may be induced *in vitro* to differentiate into numerous cell types. Studies using this leukemic cell line have been invaluable in a variety of areas. HL-60 is induced to differentiate into granulocyte-like cells by incubation with a wide variety of compounds, including DMSO and retinoic acid (11,12) or into monocyte (macrophage)-like cells by incubation with 1,25-dihydroxyvitamin D3 (VD3) or phorbol esters (13-15). Moreover, the HL-60 cell line is also capable of differentiating into eosinophilic granulocytes when cultured under mildly alkaline conditions (16). The HL-60 cell line expresses MHC class I molecules (17), but lacks the expression of MHC class II and costimulatory molecules (18). The demonstrated capacity to differentiate *in vitro* into cells exhibiting numerous characteristics of various myeloid-lineage cell types proposed the sensitivity of the HL-60 cell line for differentiation along the myeloid DC pathway, whereas studies using cytokines to promote the DC differentiation of the HL-60 cell line were not successful (19,20). Treatment with cytokines did not induce the enhanced expression of costimulatory nor MHC molecules. Inclusion of calcium ionophore (CI) mobilization treatment resulted in a more mature phenotype: CI induced the HL-60 cell line to upregulate CD83 and CD86 expression and to acquire dendritic processes, characteristics that are associated with the mature, activated DC phenotype. Of note, CI treatment also resulted in a marked increase in APC function, as determined by enhanced allogeneic T-cell stimulation capacity. However, the T-cell stimulatory capacity was low, as CI treatment failed to induce MHC class II molecules and downregulate MHC class I molecules. HL-60 cells only upregulated the expression of MHC class II molecules when induced with a combination of ionophore and inteferon-γ. The mechanism by which CI induced the differentiation of HL-60 cells into DCs was related to triggering a downstream signal transduction pathway. Protein kinase C (PKC) plays a role in determining the capacity of CI to induce leukemic cell differentiation and the blockade of PKC with bisindolylmaleimide-I (Bis-1) inhibited the differentiation of HL-60 myeloblasts into leukemic DCs with CI (21,22).

3. NB4 cells

The NB4 cell line, a human promyelocytic leukemia cell line, is the only permanent cell line with t(15;17) established from the leukemic cells of a patient with APL. The t(15;17) translocation produces a chimeric protein called PML-RARα (23). NB4 cells were instrumental in the molecular characterization of the PML-RARα fusion gene (24). Although HL-60 was previously known as 'promyelocytic', it has since been revealed that it was derived from an acute promyelocytic leukemia with maturation (M2). Moreover, it does not contain the typical t(15;17) translocation (25). NB4 cells undergo differentiation via the granulocytic pathway when exposed to all-trans retinoic acid (ATRA) (23). ATRA mediates its effect via specific nuclear retinoid receptors (26). The further differentiation of leukemic promyelocytes into DC-like cells following their differentiation into granulocytes by ATRA has also been studied (24). The differentiation of NB4 cells by ATRA causes the cells to express DC markers that enable ATRA-differentiated NB4 cells to present antigens to, and hence activate, T cells. NB4 cells upregulate the markers identified in DCs, including HLA-DR, costimulatory molecules (CD80 and CD86), adhesion molecules (CD40) and chemokine receptors (CCR6) in the presence of ATRA. High levels of expression of CD83, a specific surface marker of DC maturation (27), were also detected on the surface of ATRA-treated NB4 cells. The mechanism by which ATRA-differentiated NB4 cells are induced into DC-like cells involves the NF-κB pathway (28,29). Previous research has demonstrated that phosphatidic acid (PA) also differentiates the NB4 cells into DC-like cells (30). The expression of DC markers, including MHC-II, CD11c, CD80 CD86 and CD83, was reported to be upregulated in PA-treated NB4 cells (30). Increased functional capacities were also revealed in PA-differentiated NB4 cells with regard to changes in T-cell proliferation, cytokine production, endocytic activity and cytolytic capacity. The downregulation of PML-RARα or related signaling pathways, including ERK, may mediate the differentiation signals in the NB4 cells exposed to PA. However, further research is required to identify the downstream target of ERK-1/2 that is involved in the PA-induced differentiation of NB4 cells into DC-like cells.

4. MUTZ-3 cells

The human acute myelomonocytic leukemic cell line MUTZ-3 may provide an alternative model for DC studies. Several previous publications have proposed that a proportion of MUTZ-3 cells exhibit the phenotypic and morphological characteristics that resemble those of DCs and that these cells undergo further maturation and acquire the ability to activate resting T cells (31,32).

MUTZ-3 is a human myeloid leukemia cell line established from a 29-year-old male, which carries the inv(3)(q21q26) and the t(12;22) (p13;qll) chromosomal rearrangements (33). It exhibits the morphological and phenotypical characteristics of monocytes, as suggested by its expression of monocyte-specific esterase and myeloperoxidase enzymes and the expression of the monocytic marker CD14. The MUTZ-3 cell line consists of three distinct subpopulations, a proliferating pool of small $CD34^{+}CD14^{-}CD11b^{-}$ progenitors, which differentiate through an intermediate $CD34^{-}CD14^{-}CD11b^{+}$ stage to ultimately give rise to a morphologically large, more differentiated, nonproliferating $CD14^{+}CD11b^{hi}$ precursor population during cytokine-dependent culture. This maintained capacity has been described to be cytokine-dependent for its proliferation and survival (33). Masterson *et al* have demonstrated that MUTZ-3 cells have the potential to differentiate into Langerhans-like cells upon the addition of a cocktail of differentiating cytokines (34). Over the course of MUTZ-3 differentiation, cytokine receptors that are associated with DC differentiation, including GM-CSF-R and TNF-R, are upregulated (35). The MUTZ-3 cell line has been shown to downregulate CD14 in response to GM-CSF and IL-4 and to exhibit the characteristics of CD34-derived DC precursors (34), showing a unique potential for the phenotypical differentiation into functional DCs with discrete immature and mature stages. Culturing MUTZ-3 cells in GM-CSF, IL-4 resulted in proliferation arrest, cell differentiation and the neoexpression of CD1a. The culture of MUTZ-3 iDCs with high TNFα induced the neoexpression of the DC maturation marker CD83 with further upregulation of CD1a. MUTZ-3-derived DC (MuDC) maturation was also induced by CD40-mediated stimulation and demonstrated a high level of expression of HLA class II molecules, CD80 and CD86 (36). It has been further demonstrated that MuDCs possess the capacity to acquire a functional cytokine-induced DC phenotype, which exhibits the full range of functional antigen-processing and presentation pathways and exhibits functional properties that are essential for the *in vivo* generation of cytotoxic T lymphocyte (CTL)-mediated immunity (37,38). Signals that promote DC maturation and survival may follow various pathways. It has been shown that the maturation of DCs is mediated by the activation of p38-mitogen-activated protein kinase (MAPK) (39).

Furthermore, on the basis of the comparative functional and transcriptional profiles of MuDCs and monocyte-derived DCs used as a standard source of DCs, MUTZ-3 exhibited a gene induction similar to that of monocyte-derived DCs (31).

The ability to differentiate into DCs has led scholars to investigate the MUTZ-3 cell line as a potential *in vitro* model for the identification of skin allergens (40,41). Indeed, the immortalized human MUTZ-3 cell line constitutes an unlimited supply of DC precursors and is a potentially useful tool for the generation of stable transfectants for the further elucidation of DC differentiation pathways.

5. THP-1 cells

THP-1 is a human monocytic leukemia cell line that was cultured from the blood of a 1-year-old male with acute monocytic leukemia (42). THP-1 has been used not only as a clinical model of a leukemic cell, but also as a scientific model of differentiation in response to various stimuli. On stimulation with phorbol 12-myristate 13-acetate (PMA) or VD3, which activates PKC, THP-1 cells cease proliferation, become adherent and differentiate into macrophage-like cells (43). IL-32 also induces the differentiation of the THP-1 cells into macrophage-like cells, the expression of CD1a, a DC marker, and amplifies the effects of GM-CSF/IL-4 on CD83 expression. These observations demonstrate that IL-32 induces the differentiation of monocytes into a phenotype that exhibits an increase in certain DC markers. The effect of IL-32 on monocyte differentiation appears to be dependent on caspase-3 activity (44). Moreover, previous studies have identified that the THP-1 cell line is differentiated rapidly into mature DCs when cultured in serum-free medium containing GM-CSF, TNF-α and ionomycin (45).

Generally, only the use of a serum-free medium complemented with GM-CSF and TNF-α results in the differentiation into iDCs. The culturing of THP-1 cells in a serum-free medium supplemented with ionomycin resulted in a complete differentiation of the cells into mDCs (45). These THP-1 cell line-derived highly pure DCs exhibit the morphological, phenotypical, molecular and functional properties, including characteristic DC morphology and cell-surface molecule expression profiles, as determined by the cell-surface expression of CD83, CD80, CD86, CD40, CD206, CD209, CD120 (46,47), endocytotic activity (48,49) and strong T-cell stimulatory capacity (50,51). Ionomycin is a CI that mediates the intracellular calcium flux by increasing the cell membrane permeability to Ca^{2+}. Mobilization of intracellular calcium has been shown to activate the signaling pathways known to be induced in response to cytokine stimulation and finally converges on the activation and nuclear translocation of transcription factors of the NF-jB/Rel family, leading to DC maturation (52,53).

6. K562 cells

The K562 cell line was originally established from a pleural effusion of a patient with chronic myelogenous leukemia in terminal blast crisis (54), which exhibits the Philadelphia (Ph) chromosome, an aberration involving a 9:22 chromosomal translocation identified in >90% of chronic myelogenous leukemia cases (55). These cells exhibit erythroid, granulocytic, monocytic or megakaryocytic markers (56), which suggests that they may result from the transformation of a multipotential hematopoietic precursor. K562 cells have been extensively used as an *in vitro* model system for studying the differentiation along the erythroid lineage. Following treatment with hemin, 5-azacytidine, l-/3-D-arabinofuranosylcytosine, daunomycin or erbimycin, the cell line is induced to differentiate into an erythroid lineage (57-59). By contrast,

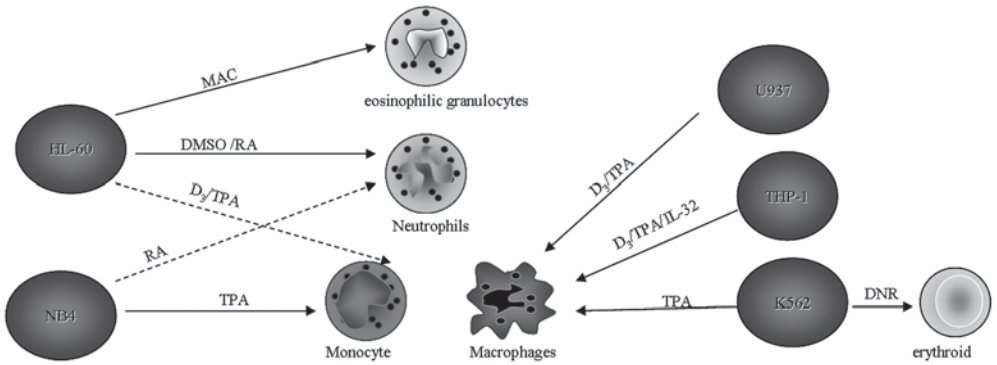

Figure 1. Schematic diagram illustrating trans-lineage differentiation of HL-60, NB4, U937, THP-1 and K562 cells. MAC, mild alkaline conditions; RA, retinoic acid; DMSO, dimethyl sulfoxide; TPA, 12-*O*-tetradecanoylphorbol-13-acetate; DNR, daunomycin.

phorbol dibutyrate and phorbol 12-myristate 13-acetate (TPA) induce differentiation into monocytes (60).

In addition, upon stimulation with PMA plus TNF, K562 cells develop DC-like cytoplasmic projections, but the expression of typical DC markers, including CD86, CD40 and CD83, remains low. However, PMA plus A23187 was found to induce differentiation into cells with typical DC morphology, characteristic surface markers (MHC class I, MHC class II, CD86, CD40, CD83), chemokine and transcription factor expression and the ability to stimulate T-cell proliferation. The mechanisms underlying this differentiation process concerned with the downregulation of BCR-ABL gene expression specifically involve downstream signaling through the MAPK pathway (61).

7. Concluding remarks

DCs play a fundamental role in modulating the innate and adaptive immune responses. Thus, they have evoked considerable interest as potential tools for the development of cell therapies to induce antitumor immune responses. There has therefore been enormous interest in understanding the function of these cells and in applying this to immunotherapy. DCs may be isolated as terminally differentiated, post-mitotic cells from all tissues and in the blood, but they comprise only a small proportion (less than 0.1% of circulating leukocytes). DCs may also be obtained from adherent peripheral blood monocytes and $CD34^+$ stem cells *in vitro*. The relatively low numbers of cells that may thus be obtained, compared with the difficulties: laborintensity and reproducibility associated with the study of primary human material *in vitro* and *in vivo*, have seriously hampered studies aimed at exploring the cell biology of DCs. Studies of human DCs have been constrained by such difficulties, therefore the majority of studies have been carried out using *in vitro* model systems. These model systems have proved extremely powerful, generating a large body of fundamental research describing numerous aspects of DC function, alongside a body of translational research using DCs for the cellular adoptive immunotherapy of infection and cancer.

A number of cell lines exhibiting the characteristics of DCs would allow for the detailed study of DC differentiation without the associated problems. Leukemic cell lines retain a degree of lineage plasticity and a number differentiate further in response to defined stimuli. Moreover, trans-lineage differentiation among erythroid, myeloid, megakaryocytic and lymphoid compartments have been also reported *in vitro* in the presence of selected cytokines or chemicals (Fig. 1) (62). This suggests that myeloid leukemias retain the potential for terminal differentiation into various peripheral mature cell types. Therefore, the flexible ability allows the leukemic cells to share a potential for differentiation into DCs.

The potential to differentiate into DCs has already been studied for several cell lines. Using diverse combinations of cytokines and hematopoietic differentiation agents, various human hematopoietic cell lines have the ability to differentiate into iDCs and mDCs with the phenotypic, molecular and functional properties of DCs. These model systems have proven extremely powerful, generating a large body of fundamental research describing numerous aspects of DC function, alongside a body of translational research using DCs for the cellular adoptive immunotherapy of infection and cancer.

Leukemia cell lines were predicted to be good candidates for differentiation into DCs, although MUTZ-3 is unique in comparison with other myeloid leukemic cell lines (45,63) in that it allows the study of discrete transitional stages in myeloid DC development. No single cell line is likely to provide a perfect model for a normal cell phenotype. In spite of their limitations, a number of DC model cell lines may be successfully used to study significant aspects of DC biology *in vitro*. The MUTZ-3 cell line thus represents a valuable and sustainable model system for the further elucidation of the molecular mechanisms regulating the early and late stages of human myeloid DC differentiation.

We expect that the proper use of DC model cell lines may aid in the revelation of significant new insights into DC development, maturation, physiology and pathology that may subsequently be applied to improve the application of DCs in the clinic.

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