REVIEW

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Counteracting the enzymatic activity of dipeptidylpeptidase 4 for potential therapeutic advantage, with an emphasis on cord blood transplantation

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Dipeptidylpeptidase (DPP) 4, also known as CD26, is an enzyme present on the surface of a number of different cell types. It is also found within cells and as a soluble protein in body fluids. It can specifically truncate proteins at the penultimate N-terminus residue for some amino acids, such as alanine, proline, serine, and perhaps others. DPP4 has been implicated in regulating the *in vitro* and *in vivo* functional activities of a number of hematopoietically active molecules, and this information, along with that on inhibition of DPP4, has been studied in efforts to enhance hematopoietic cell transplantation (HCT), hematopoiesis after stress in mouse models, and in the clinical setting of single-unit cord blood (CB) HCT. This article reviews the current status of this compound's effects on regulatory proteins, the field of CB HCT, a potential role for modulating DPP4 activity in enhancing single-unit CB HCT in adults, and future aspects in context of other cellular therapies and the area of regenerative medicine.

Keywords: Dipeptidyl peptidase 4; Hematopoietic stem cell transplantation; Cytokines; Tissue therapy; Regenerative medicine

INTRODUCTION

Hematopoietic cell transplantation (HCT) is a well-documented and proven life-saving treatment for patients with malignant and nonmalignant disorders in need of cellular replacement therapy with healthy autologous or allogeneic hematopoietic stem cell (HSC) and hematopoietic progenitor cell (HPC) [1]. HSCs and HPCs are tissue-specific stem cells that are found in and collected from the bone marrow (BM) or cytokine-mobilized peripheral blood (mPB) of adults and children, or umbilical cord blood (CB) [2,3]. Immature HSC and HPC populations allow for blood cell replacement after HCT. Other types of cellular replacement therapy have the potential to be options in the context of the new and rapidly emerging field of regenerative medicine. Cells considered of value in regenerative medicine include embryonic stem cells, induced pluripotent stem cells, and various other tissue-specific stem and progenitor cell populations [4], such as those from non-hematopoietic tissue such as muscle and nerves. While it is not yet clear whether cellular replacement therapies using populations other than HSCs and HPCs for HCT have resulted in cures or significant health benefits [4], there is optimism that continued scientific and clinical efforts in the area of regenerative medicine will demonstrate such clinical benefits in the future. Many investigators worldwide are devoting efforts to this endeavor.

The functional characteristics and capacities of the

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different stem and progenitor cell populations, which include self-renewal (the capacity of these early immature cells to make more of themselves, a function usually reserved for and linked to stem cells rather than progenitor cells), survival, proliferation, differentiation, and movement (migration, homing), are in part regulated by proteins such as cytokines and chemokines (a subset of cytokines) as well as other growth-modulating biomolecules such as hormones [3,5]. Most studies of protein regulation in stem and progenitor cell functions focus on specific protein-receptor interactions at the surface of the cells, and the subsequent intracellular signaling transduction events and cell biological effects triggered by the interaction [5]. However, little previous effort has gone into how modification of a protein itself can influence cell regulation, and what role specific enzymes may play in the resulting protein—cell signaling events.

This review focuses on the enzyme dipeptidylpeptidase 4 (DPP4); how it modifies the functional effects of proteins with demonstrated or putative DPP4 truncation sites in the regulation of HSCs, HPCs, and hematopoiesis; and how this modification may influence other cellular systems, in the context of regenerative medicine. Another focus is on CB HCTs, and on the potential role for DPP4 inhibition in enhancing engraftment of CB HSCs and HPCs in the clinical setting, a possible paradigm for also enhancing the engraftment of other cell types.

CB HSCs, HPCs, AND HCT

CB is now a well-accepted source of transplantable HSCs and HPCs and has been used to treat more than 30,000 patients with a wide assortment of malignant and nonmalignant disorders [1,6]. It has been and can be used to treat largely the same array of disorders treated by BM or mPB HCT. It was first used in a setting of human leukocyte antigen (HLA)-matched sibling CB HCT [7,8], and subsequently for partial HLA-matched siblings, but most CB transplants are now done in a partially HLA-matched unrelated allogeneic setting [1].

The concept and scientific basis for CB HCT are based on laboratory studies that have show in detail the biological properties of these cells, and their efficient collection, transportation, processing, and cryopreservation as well as the recovery of thawed cells stored in a frozen state [9]. Since these laboratory studies, there have been follow-up studies on the biology of CB HSCs and HPCs [10-16], and the efficient recovery of these cells after 5 [12], 10 [17], 15 [18], and 23.5 years of storage [19] in the author's laboratory, which has served as the first proof of principle CB bank from which came the first five, and two of the next five, CB collections used for HLA-matched sibling CB HCT.

There are advantages to using CB as a source of HSCs and HPCs for HCT, compared to BM or mPB [1,6], including ease of collection, with no damage or harm to the baby or mother, the long-term storage of these cells in CB banks and thus rapid availability of these collections for patients, especially when such cells are needed in a quick and timely fashion for HCT because of the progressive nature of the disease and the more naïve status of the immune cells within CB that has allowed for less rigorous HLA-matching and less graft-versus-host disease than that elicited by BM or mPB.

There are, however, also disadvantages in using CB for HCT [1,6]. One such concern includes the slower time to recover neutrophils, platelets, and immune cells that may result from the finite number of cells one can collect at the birth of the baby, compared to what can be collected from BM or mPB. This problem is also a concern for use of CB HCT in adult patients who require more cells than children for engraftment. A number of laboratories worldwide are looking at ways to address these disadvantages [1,6,20]. This includes the use of two collections of CB, *ex vivo* expansion of CB HSCs and HPCs, intrafemoral injection of CB, and the enhancement of the homing and engrafting capability of CB HSCs and HPCs for more efficient CB HCT. Towards this aim, for over 10 years, we have been investigating a role for modulating DPP4 activation and expression in the homing and engrafting capabilities of HSCs and HPCs. Our work, and that of others, in this effort are noted below.

DPP4/CD26 AND HSCs, HPCs, AND CB HCT

DPP4, a member of the family of prolyl oligopeptidases

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[21], functions as a serine protease that can selectively cleave at the penultimate amino acid from the N-terminus of a protein, with degrees of specificity inherent in this truncation depending on whether that amino acid is proline or alanine or perhaps some other amino acid such as serine [22]. DPP4 can be found on the surface of certain cells, where it is also referred to as CD26 [23], but it is also found within cells [24] and as soluble enzyme in serum, plasma, and other body fluids [25,26].

The chemoattractant chemokine stromal cell-derived factor (SDF)-1/CXCL12 has a DPP4 truncation site, and we demonstrated that DPP4-truncated SDF-1/CXCL12 lost its significant chemotactic (directed cell movement) effect on HPCs. In addition, the DPP4-truncated inactive SDF-1/CXCL12 blocked the chemotactic activity of the full-length form of SDF-1/CXCL12 [27]. Moreover, we were able to enhance the chemotaxis of HPC to SDF-1/CXCL12 by pretreating target cells with small peptide inhibitors of DPP4 (e.g., the tripeptide diprotin A Ile-Pro-Ile [27] or the dipeptide Val-Pyr) or using CD26 knock-out (-/-) mouse BM cells [28] before adding the SDF-1/CXCL12 to the target cells. This led to our studies demonstrating that $CD26^{-/-}$ mice [29] or mice pretreated with the DPP4 inhibitor diprotin A [30] were less responsive than control mice to the HPC-mobilizing effects of granulocyte (G)-colony stimulating factor (CSF) [29,30]. The next studies from our group demonstrated that $CD26^{-/-}$ mouse BM cells, or BM cells pretreated with diprotin A or Val-Pyr, had increased homing efficiency and engrafting capability in lethally irradiated primary recipient congenic mice in both competitive and noncompetitive transplantation assays, and greater secondary repopulating capacity in a noncompetitive assay of lethally irradiated mice, than that of control BM cells [28]. This was associated with enhanced engraftment at both higher and limited doses of donor cells. Thus, deletion of CD26 in $CD26^{-/-}$ mice or inhibition of DPP4 (with two separate DPP4 inhibitors) demonstrated increased homing of a long-term BM repopulating and self-renewing HSCs [28]. This work was quickly confirmed and extended by others [31-33], followed by reports [34-36] demonstrating that inhibition of DPP4 on $CD34^{+}$ human CB or human mPB enhanced their engrafting capability in sublethally irradiated mice with nonobese diabetic severe combined immunodeficiency (SCID). This mouse serves as an *in vivo* model for detecting human HSCs, which are quantitated as SCID-repopulating cells. Thus, the engrafting capability of mouse BM and human CB or mPB cells could be enhanced significantly by deletion or inhibition of DPP4 [34-36]. These data, plus information suggesting that inhibition of DPP4 activity in recipient mice could also enhance the engrafting capability of mouse BM cells in a lethally irradiated congenic mouse model of HCT [24], led our group to conduct a pilot study that evaluated the role of DPP4 inhibition in patients receiving CB HCT [37].

This pilot study evaluated the impact of an orally active small molecule inhibitor of DPP4 (sitagliptin; U.S. Food and Drug Administration-approved for use in treating type II diabetes) on the engraftment of single-unit CB in adult patients with end-stage hematological malignancies (leukemia and lymphoma) [37]. While most studies on CB HCT in adults have used double CB HCT, we felt that this was not necessary because we were using single CB units that met the estimated requirement for numbers of nucleated cells per kg body weight needed for engraftment of adults, and the use of single CB HCT would not complicate the interpretation of results inherent to the use of double CB HCT, in which case only one of the two CB units usually wins out for long-term engraftment, especially because the characteristics of the winning CB unit cannot yet be predicted [1]. We chose to assess the effects of engraftment using treatment of the recipient rather than the donor cells because sitagliptin is orally active and could be administered as a pill. Based on the reported safety of sitagliptin administered in this fashion to healthy adults [38], the kinetics of inhibition of DPP4 in these adults, which resulted in rapid and near-complete DPP4 inhibition that lasted up to 24 hours [38], and our belief at the time that the results of our enhanced mouse BM and human $CD34^{+}$ CB engraftment in mouse studies were due to inhibiting DPP4, which prevented the truncation and inactivation of the homing/chemotactic chemokine SDF-1/CXCL12 [28], we chose to administer the pill once a day for only 4 days, starting 1 day prior to the CB unit, and on the day of the CB unit infusion, as well as for 2 days after the infusion [37]. We felt that this should be sufficient time for the SDF-1/CXCL12 homing and initial engrafting process to occur. For the 17 patients who received red blood cell-

depleted CB units and sitagliptin in this dosing regimen, the median time to neutrophil engraftment was 21 days. While we do not have proof that this was a significantly improved time for neutrophil engraftment for CB HCT, the results were encouraging compared to the engraftment reported by others [39] for single-unit CB HCT in context of the numbers of cells used, HLA disparity, and the extent of disease and clinical status of recipients. We do believe that the engraftment capacity of single-unit CB HCT can be improved to a much greater extent than we have reported [37] by modifying the dose schedule sitagliptin, for the following reasons. First, it became apparent during the clinical study that sitagliptin given once a day was not as effective for reducing the DPP4 enzyme activity in our patients [37] as it was in normal volunteers [38], in that the inhibition of DPP4 activity in our patients was only apparent for the first 4 to 8 hours after the administration of sitagliptin, compared to more than 24 hours inhibition seen in the normal volunteers. This decrease and rapid return of DPP4 activity was similar for each of the 4 days of sitagliptin administration. Thus, we have begun to administer sitagliptin every 12 hours for 4 days and are beginning a multicenter trial using this dosing schedule, because preliminary studies demonstrated more prolonged DPP4 activity inhibition with the twice versus once a day administration of sitagliptin. It is not yet clear why administration is less effective at once a day. It may be that the chemotherapy and radiation given to our patients caused increased cell release of DPP4 because of cell death [24], thus requiring a more frequent dosing schedule to provide more effective DPP4 inhibition. Our more recent studies, discussed below, also alerted us to the fact that DPP4 could truncate and decrease the activities of a number of CSF molecules, which may be involved in nurturing the engrafting and blood cell-repopulating capacity of donor CB cells [24]. Thus, future clinical studies may need to assess sitagliptin administration for longer than 4 days, in addition to the increased frequency of administration of this DPP4 inhibitor. Next generation DPP4 inhibitors may also be more efficacious in *in vivo* DPP4 inhibition. Such studies must be performed with a focus on the safety of patients. As discussed in more detail later in this review, there are likely going to be uses for DPP4 modulators in other clinical situations involving different stem and progenitor cells, and more mature cells of different tissues and organs [40,41].

EXPANDED ROLES FOR DPP4

In addition to the effects of inhibition of DPP4 on SDF-1/CXCL12 functions of chemotaxis and homing, we recently reported similar effects on other functions of SDF-1/CXCL12, including enhanced survival of HPCs and enhanced cytokine-induced *ex vivo* expansion of HPCs [24]. DPP4-truncated SDF-1/CXCL12 had no significant effect on these functions, and inhibition of DPP4 enhanced them. These effects were extended to members of the CSF family, including G-CSF, granulocyte macrophage (GM)-CSF, interleukin (IL)-3, and erythropoietin (EPO) [24]. Treatment of target cells with inhibitors of DPP4 (e.g., diprotin A) greatly enhanced the CSF activities of G-CSF, GM-CSF, IL-3, and EPO on colony formation by human CB and mouse BM cells *in vitro* as well as the *in vivo* activities of GM-CSF or EPO [24]. Inhibitors of DPP4 had no significant effect on the activities of other hematopoietically active cytokines such as macrophage (M)-CSF or on those of the potent costimulating cytokine stem cell factors or Flt3-ligand, which do not have putative DPP4 truncation sites [24]. Because members of the CSF family that have DPP4 truncation sites may be involved in the cytokine storm elicited during recovery of mice after stresses such as chemotherapy or radiation, we evaluated whether increased DPP4, which we noticed after mice were given radiation [24], might dampen the rebound in hematopoiesis seen after low and higher nonlethal doses of irradiation, and also after administration of 5-flurouracil (5FU) or other chemotherapeutic drugs. In this context, we found that $CD26^{-/-}$ or inhibition of DPP4 was associated with a faster and higher level of hematopoietic recovery after 5FU and 400 or 650 cGY gamma irradiation [24]. This, and the enhanced effectiveness of *in vivo* administration of GM-CSF or EPO to mice with decreased or absent DPP4 activity [24], plus the enhanced engrafting capabilities of mouse BM cells in lethally irradiated $CD26^{-/-}$ congenic mice or congenic mice pretreated with sitagliptin [24] demonstrated how downmodulation of DPP4 can have a positive effect on both preclinical and clinical models of HSCs.

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A search for other regulatory proteins with putative truncation sites identified numerous proteins that are known to have significant influences in many different cell, tissue, and organ systems [24,40,41]. An extensive but certainly not an all inclusive list of such proteins can be found in our recent review article [40]. This list suggests how DPP4 and its up- or down-modulation may be useful for better understanding protein regulation in many different systems, as well as for possible preclinical and subsequent clinical advantage. As our previous reviews point out [40,41], the identification of putative DPP4 truncation sites in proteins does not prove that these are true truncation sites, and even if these are shown to be true truncation sites, the consequences of DPP4 truncation on the functional capacity of each individual protein will need to be determined experimentally, because there are many different possible scenarios for DPP4 truncation of proteins [40,41], with inhibition or enhancement of function. Once these different actions are worked out for each protein, it will be necessary to determine how the truncated molecule is acting at a mechanistic level, and how modulation of this may influence the different possible functional activities of these proteins, and then whether and how this information may be useful for potential therapeutic benefit. A recent paper reported that sitagliptin enhanced the numbers of circulating angiogenic cells and angiogenesis [42], although the exact protein player(s) and mechanism(s) involved in this have not yet been identified.

CONCLUSIONS

DPP4 has been shown to directly influence the actions and potency of a number of different proteins that have regulatory activities in HSCs, HPCs, and hematopoiesis. Inhibition or functional deletion of DPP4 has resulted in enhanced protein activities *in vitro* and *in vivo* in preclinical models, and has been used with encouraging although not yet definitive results for enhancing the engrafting capability of limited numbers of CB cells in the context of a pilot study that evaluated CB HCT in adult patients with end-stage hematological malignancies [37]. It is clear that DPP4 will likely have far-reaching effects on our improved understanding of the activities of a plethora of proteins and their regulation in different cell, tissue, and organ types. Understanding the roles of DPP4 in protein actions in these different systems may prove to be of use and benefit in HCT and in ongoing efforts to more clearly define the fields of non-HCT and regenerative medicine, and the possible clinical benefits of modulating DPP4. It is also likely that other enzymes will be found to be important for modulating protein function [24], information that would be of academic and potentially clinical utility.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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