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Autore/i: Tiberio L, Del Prete A, Schioppa T, Sozio F, Bosisio D, Sozzani S

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REVIEW

Chemokine and chemotactic signals in dendritic cell migration

Laura Tiberio[1], Annalisa Del Prete[1,2], Tiziana Schioppa[1,2], Francesca Sozio[1,2], Daniela Bosisio[1] and Silvano Sozzani[1,2]

Dendritic cells (DCs) are professional antigen-presenting cells responsible for the activation of specific T-cell responses and for the development of immune tolerance. Immature DCs reside in peripheral tissues and specialize in antigen capture, whereas mature DCs reside mostly in the secondary lymphoid organs where they act as antigen-presenting cells. The correct localization of DCs is strictly regulated by a large variety of chemotactic and nonchemotactic signals that include bacterial products, DAMPs (danger-associated molecular patterns), complement proteins, lipids, and chemokines. These signals function both individually and in concert, generating a complex regulatory network. This network is regulated at multiple levels through different strategies, such as synergistic interactions, proteolytic processing, and the actions of atypical chemokine receptors. Understanding this complex scenario will help to clarify the role of DCs in different pathological conditions, such as autoimmune diseases and cancers and will uncover new molecular targets for therapeutic interventions.

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INTRODUCTION

The appropriate localization of dendritic cells (DCs) is a crucial step in the regulation of the immune response and plays a fundamental role in both steady-state and pathological conditions[1,2]. Based on developmental origin, committing transcription factors, and surface markers, DCs are classified as classical or conventional DCs (cDCs), plasmacytoid DC (pDCs), and monocyte-derived DCs (moDCs)[3]. DCs are at the interface of innate and acquired immunities since they sense invading pathogens, provide co-stimulatory signals, and trigger specific immune defenses[4,5]. In homeostatic conditions, a heterogeneous population of immature DCs with sentinel functions resides in the peripheral tissues. Upon early recognition of pathogens or exposure to inflammatory cytokines, DCs induce a tailored activation of innate and adaptive effector cells to face the pathogens. Specific subsets of DCs recruit and activate innate lymphoid cells and natural killer cells through the rapid secretion of cytokines[5,6]. As potent antigen-presenting cells, DCs also take up antigens and migrate to draining lymph nodes, where they promote T-cell and B-cell responses[7–9]. Conversely, a constitutive trafficking of DCs from noninflamed tissues to lymph nodes maintains the tolerance against self-antigens[10].

DC migration is a tightly regulated process, controlled by a large variety of chemotactic factors, of which chemokines play a fundamental role[11,12]. Chemokines are small, secreted proteins with conserved sequences and structural features. Chemokines are classified into four families based on the relative position of a conserved cysteine motif, namely, CC, CXC, XC, and CX3C[13]. Chemokines can also be classified as homeostatic and inflammatory proteins, although some of them (e.g., CCL21 and CXCL12) may have both homeostatic and inflammatory functions[14]. Chemokines regulate migration, adhesion, phagocytosis, cytokine secretion, proliferation, and apoptosis by activating G-protein-coupled receptors (GPCR)[13]. In addition to the classic chemokine receptors, there is a subset of chemokine receptors that do not possess canonical signaling and that are endowed with scavenging functions. This subset of receptors is called the atypical chemokine receptors (ACKR). ACKRs are at the forefront of research for their ability to regulate the inflammatory response by different mechanisms[13,15–17]. This article focuses on chemokines and other chemotactic factors as key molecules for DC migration and function, with a special emphasis on the multiple levels of regulation by the chemokine system.

The chemokine system in DC biology

Most precursors of DCs leave the bone marrow and enter the circulation to localize to lymphoid and nonlymphoid tissues. In both steady-state and inflammatory conditions, resident, peripheral tissue DCs travel via the lymphatic system to draining lymph nodes, where they interact with T lymphocytes[4]. Human pDCs are usually found only in the circulation and in primary and secondary lymphoid organs where they are likely to localize in a CXCR4-dependent and ChemR23/CMKLR1-dependent manner. Under pathological conditions, pDCs localize to peripheral tissues, including the skin, some tumors, and atherosclerotic aortas by mechanisms that are possibly dependent on CXCR4, CXCR3, and CMKLR1 expression[18,19]. In mice under both homeostatic and inflammatory conditions, chemokine receptors such as CCR2, CCR5, and CCR9, regulate the migration of pDCs to lymphoid and nonlymphoid organs, such as the small intestine and skin[18]. To travel such different migratory routes, DCs rapidly change chemokine receptor expression to respond to the chemotactic gradient guiding them to their correct position[20]. A survey of chemokine receptors and their role in the migration of mouse and human DCs is shown in Tables 1 and 2, respectively.

The identities of the chemokines responsible for the egression of DC precursors from the bone marrow, as well as those that mediate their homeostatic recruitment into nonlymphoid tissues, are poorly characterized. Mice lacking CXCR4 in CD11c^{+} DC precursors show a significant decrease in bone marrow pre-DCs,

[1]Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy and [2]Humanitas Clinical and Research Institute, Rozzano-Milano, Italy
Correspondence: Silvano Sozzani (silvano.sozzani@unibs.it)
These authors contributed equally: Laura Tiberio and Annalisa Del Prete.

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Table 1. The expression and functions of chemokine receptors in mouse DC subtypes

DC subtypes	Chemokine GPCR	Major functions	References
cDC	CCR1	Recruitment into the lungs during allergic reactions	105
	CCR2	Central tolerance	106
	CCR2, CCR6	Migration to inflamed tissue (immature)	107
	CCR2, CX3CR1	Positioning in the lung	21
	CCR4	Emigration of cutaneous DCs to the lymph nodes	39
	CCR6, CCR1	Recruitment to Peyer's patches	108
	CCR7	Migration to lymph nodes	10
	CX3CR1	Migration to lymph vessels, LEC transmigration	37
	CXCR4	Bone marrow retention (DC precursors)	21
		Cutaneous DC transmigration across LEC	38
	CXCR5	Th2 induction	109
		Recruitment to Peyer's patches	110
	XCR1	CD8 + T-cell priming and activation	111
		Central tolerance induction	112
		Intestinal immune homeostasis	113
pDC	CCR2	Homeostatic trafficking	114
	CCR2, CCR5	Bone marrow egression	115
	CCR6, CCR10	Recruitment to inflamed epithelia	116
	CCR9	Homing to the small intestine	117
		Oral tolerance	118
		Central tolerance	119
	CXCR4	Progenitor differentiation in bone marrow niches	120
	CXCR4, CCR7, and CXCR3	Spleen- and HEV-mediated lymph node entry	50,121,122

Table 2. Expression and functions of chemokine receptors in human DC subtypes

DC subtypes	Chemokine GPCR	Major functions	References
cDC	CCR2, CCR6	Recruitment to inflamed tissues	123
			124
	CCR5	Recruitment to inflamed tissues	125
	CXCR4, CCR7	Recruitment to lymph node and tonsils (in vitro activated)	47
			124
	XCR1	Antigen cross-presentation, CD8+ T-cell priming	126
pDC	CCR6, CCR10	Recruitment to inflamed epithelia	116
	CXCR3	Recruitment to diseased tissue	127
	CXCR4, CCR7	Recruitment to lymph node (in vitro activated)	47
	CXCR4	Homeostatic recruitment to lymph node	47
moDC	CCR1, CCR3	Recruitment to inflamed tissues	128
			129
	CCR1, CCR5	Recruitment to inflamed tissues	81

suggesting that CXCL12 is a bone marrow retention factor[21]. Moreover, patients with WHIM syndrome, a genetic alteration characterized by gain-of-function mutations in CXCR4, have a reduced number of circulating DC subsets[22]. Once in circulation under steady-state conditions, different receptors, including CCR2 and CX3CR1, are responsible for DC localization to the lungs and other peripheral tissues[21]. In the skin, Langerhans cells are mainly maintained by self-renewal. However, under inflammatory conditions, they can also be replenished by bone-marrow-derived precursors[23]. Immature resident DCs express several chemokine receptors but it is still unclear if retention in peripheral tissues is an active or passive mechanism.

The migration of DCs to the lymph nodes is a complex process that relies on two main chemokines, namely, CCL19 and CCL21. CCL21 is important for directing DCs toward and along lymphatic vessels while CCL19 is involved, together with CCL21, in DC migration within the lymph nodes. The expression of the cognate receptor, CCR7, is crucial for the correct positioning of DCs and for the initiation of specific immune responses[24,25]. Under resting conditions, CCL21 is constitutively released at low levels from

intracellular granules of lymphatic endothelial cells, whereas following activation, CCL21 is transcriptionally activated[26,27]. Secreted CCL21 binds the heparan sulfates present in the interstitium, leading to the formation of a haptotactic gradient. Once in the lymphatic system, DCs crawl along a CCL21 gradient until they reach larger vessels, where they are passively transported by the flow of lymph[28]. The CCL21/CCR7 axis not only promotes chemotaxis but also the arrest of DCs on the lymphatic endothelium[29]. In addition, DC migration can be amplified by the paracrine and autocrine secretion of inflammatory cytokines, which induce increased expression of CCR7 and its ligand CCL21 on DCs and lymphatic endothelial cells, respectively[30,31]. A similar mechanism is responsible for the recruitment and retention of mature DCs in Crohn's disease[32].

In lymph node sinuses, CCL19, in addition to CCL21, also contributes to DC migration[24,33]. In the lymph nodes, the confined expression of ACKR4 to the endothelial cells of the ceiling but not the floor of the sinus contributes to the formation of a CCL21 gradient (see below)[34]. The CCL21 gradient is crucial for guiding DCs to lymph node T-cell-rich areas[35]. In addition, CCR7-dependent DC migration coordinates the activation of organ-specific Tregs, thereby promoting peripheral immune tolerance[36].

Under inflammatory conditions, CX3CL1 and CXCL12 may also play a role in DC migration. Both cytokines are expressed by activated lymphatic endothelial cells and promote DC transendothelial migration[37,38]. The migration of cutaneous DCs to the skin-draining lymph nodes is regulated by the inducible chemokine CCL17 and its cognate receptor CCR4, which are involved in the pathogenesis of allergic skin inflammation[39]. In an experimental model of autoimmune encephalomyelitis, CCL17 modulates DC trafficking in the central nervous system[40].

Synergistic interactions of chemotactic factors in DC migration

The concomitant activation of multiple chemokine receptors promotes the synergistic migration of leukocyte subsets, including DCs[41–43], in vitro and in vivo. Similarly, cooperative interactions between chemokines and lipid mediators, such as platelet-activating factor (PAF), arachidonic acid, prostaglandin E2 (PGE2), and leukotriene B4 (LTB4) also occur[31,44–46]. One of the first described cooperative interactions was of human pDCs. Circulating pDCs do not respond to CXCR3 ligands, even though they express CXCR3 at high levels[47]. However, CXCR3 ligands become chemotactic in the presence of low levels of the homeostatic chemokine CXCL12[48]. A similar cooperative interaction was observed between CXCL12 and CCR7 in vivo for the constitutive migration of pDCs to the splenic white pulp[49,50]. In monocyte-derived DCs, synergism between CC and CXC chemokines was described, with CCL3 synergizing with CXCL8 and CXCL12 and CCL2 synergizing with CXCL12[42].

A similar cooperation was described between the classical nonchemokine chemotactic receptors and the chemokine receptors. Chemerin, a ligand for CMKLR1, increases the migration of immature DCs to CCL7 and formylated peptides synergized with CCL3[42]. Finally, in a model of 2,4-dinitrofluorobenzene (DNFB)-induced contact hypersensitivity, the recruitment of DCs to the draining lymph nodes was dependent on BLT1 signaling, the high-affinity receptor for LTB4. In vitro, LTB4-stimulated DCs upregulate the expression of CCL19 and CCR7 and exhibit increased migration to CCL19 and CCL21[31]. The molecular mechanisms underlying these cooperative actions may involve multiple levels of action, including (a) simultaneous activation of multiple intracellular pathways[42]; (b) agonist heterocomplex formation[51]; and (c) receptor heterodimerization[52]. Further studies are needed to fully understand the diverse levels of complexity implicated in this action.

Chemokines as relay signals in DC migration

Inflammatory signals play an important role in the amplification and persistence of the inflammatory response[45,53,54]. Relaying signals ensure that primary chemotactic agents, produced early by the invading pathogen or by damaged cells, act locally on neighboring cells and induce the production of secondary waves of chemoattractants that enhance and promote the recruitment of cells localized far from the damaged site[53] (Fig. 1). This phenomenon was initially described for neutrophils and showed that the local production of LTB4 at the injured site functions as a relay signal responsible for the attraction of waves of distant cells to the injury site[55,56]. Data suggest that this mechanism may be more generally relevant[53,54] and several examples of putative relay signals in both in vivo and in vitro models have been proposed to regulate DC migration.

In a model of allergic airway inflammation, the migration of DCs to the peribronchiolar areas is mediated by the sequential involvement of the chemotactic receptors CCR2 and CCR7 and the formylpeptide receptor Fpr2. These relaying signals were required for the correct trafficking of DCs to the draining lymph nodes and for the priming of Th2 cells[57].

In vitro, the pleiotropic cytokine activin A induces the polarization of immature human DCs and the polarized release,

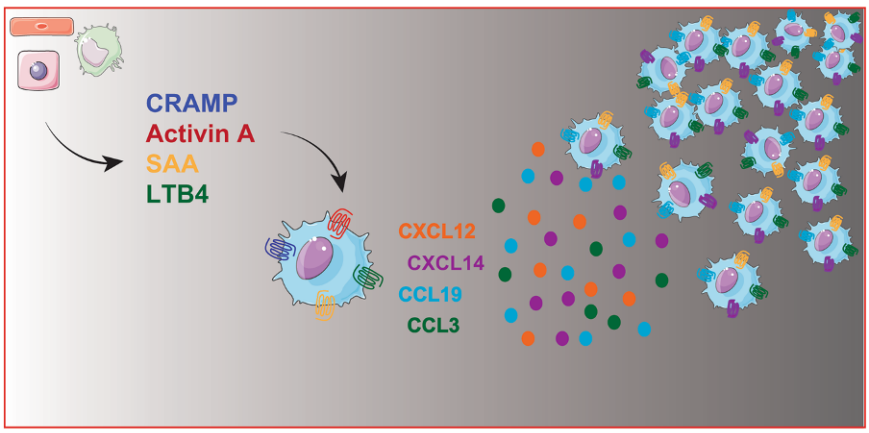

Fig. 1 Chemokines as relay signals in the migration of DCs. This cartoon depicts the different types of chemotactic signals such as DAMPs (e.g., CRAMP; cathelin-related antimicrobial peptide), acute-phase proteins (e.g., SAA; serum amyloid A), proinflammatory cytokines (e.g., activin-A), or eicosanoids (e.g., LTB4; leukotriene B4), produced by different cell types (macrophages, endothelial cells, and hepatocytes), that, in addition to directly promoting DC migration, activate migrating cells to produce chemokines that will promote a second wave of cell recruitment

at the front edge, of two CXC chemokines, namely, CXCL12 and CXCL14. The use of blocking antibodies for these two chemokines caused inhibition of activin A-induced chemotaxis[58]. Similarly, serum amyloid A, an acute-phase protein produced during inflammatory responses, indirectly amplifies the recruitment signal for DCs by the rapid secondary induction of CCL3. CCL3 is responsible for the generation of an optimal chemotactic gradient[59] (Fig. 1). Finally, CCL21 by itself may act as a relay signal to promote the CCR7-induced migration of mature DCs to the lymph nodes. There are two forms of CCL21 that differ in their ability to bind heparan sulfate and induce DC migration. They represent two distinct chemotactic signals acting in sequential waves. The full-length heparan sulfate-bound CCL21 provides the first chemotactic signal. The soluble tailless-CCL21, produced during inflammation by endogenous proteases or by activated DCs[33], represents a stronger, sustained second chemotactic signal[60].

In conclusion, the data suggest the existence of multiple levels of regulation of DC migration. These mechanisms are likely to orchestrate the sequence of signals that finely tune the recruitment of DCs to the peripheral tissues and secondary lymphoid tissues.

Atypical chemokine receptors as regulators of DC migration

Atypical chemokine receptors (ACKRs) represent a small subset of proteins that express a high degree of homology with chemokine receptors. However, ACKRs do not activate G-protein-dependent signaling or chemotactic responses[61,62]. The ACKR family includes four proteins, namely, ACKR1, ACKR2, ACKR3, and ACKR4 with ackr5 and ackr6 reserved for the receptors CCRL2 and PITPNM3, pending confirmation of their ability to bind chemokines. ACKRs regulate inflammation by acting as scavenger receptors, promoting chemokine transcytosis or regulating the formation of the chemokine gradient[15–17,62]. ACKRs regulate DC functions. For instance, ACKR2, when expressed by lymphatic endothelial cells, is able to remove inflammatory chemokines and enhances the interaction of CCR7 ligands, selectively expressed by the lymphatic vasculature, with mature DCs that have undergone CCR7 switching[63]. In addition, in a model of experimental autoimmune encephalomyelitis, ACKR2 deficiency is responsible for the reduced local accumulation of DCs and impaired T-cell priming[64,65]. As mentioned previously, ACKR4 controls the emigration of DCs from the subcapsular sinus to the lymph node parenchyma, regulating the formation of CCL19 and the CCL21 gradient[35]. Finally, the expression of ACKR4 by skin stromal cells is involved in the CCR7-dependent migration of DCs, both under steady-state and inflammatory conditions[34].

CCRL2 (ackr5) represents a paradigmatic example of regulation of the immune response by atypical chemotactic receptors[66]. In a model of OVA-induced lung hypersensitivity, CCRL2-deficient mice are defective in the induction of Th2 responses. Defective T-cell priming directly correlates with the impaired migration of antigen-loaded lung DCs to the mediastinal lymph nodes[67]. In neutrophils, CCRL2 forms heterodimers and regulates CXCR2 signaling[68]. These data suggest that this mechanism applies to other receptors and that CCRL2 might regulate the function of CCR7 in mature DCs. Moreover, CCRL2 binds to the endothelial cell barrier and presents chemerin, a chemotactic peptide, which promotes the transmigration of DCs across the endothelial cell monolayer[69,70].

Nonchemokine chemotactic factors in DC migration

More than just chemokines are involved in DC trafficking. Several nonchemokine agonists, released at inflammatory sites, promote the recruitment of DCs or their precursors[11]. These chemotactic stimuli include bacterial components, bioactive lipid mediators, and tissue danger signals (Table 3); thus, their actions may temporally precede chemokine production[11]. For instance, DCs express Fpr1 and Fpr2, two functional receptors for formylated peptides and damage-associated molecular patterns (DAMPs)[71]. Fpr2 and one of its endogenous ligands, cathelin-related antimicrobial peptide (CRAMP), is involved in DC activation and accumulation during allergic airway inflammation[57,72]. Another DAMP, the nuclear protein high-mobility group box 1 (HMGB1), regulates DC migration and function by a RAGE-dependent pathway[73]. Components of the complement cascade, such as C3a, C5a,[71,74,75] and C1q[76,77] have chemotactic functions for DCs both in vitro and in vivo. Nucleotide sensing by the purinergic receptors P2YR and P2XR regulates the DC chemotactic response[78]. Degradation of ATP to adenosine by the ectonucleotidase CD39 represents a way for regulatory T cells to induce DC migration[79]. Finally, components of the coagulation cascade, such as plasmin, regulate DC accumulation in atherosclerotic lesions[80].

Table 3. Nonchemokine chemotactic factors for DC migration

Nonchemokine agonists	Nonchemokine receptors	References
Chemerin	ChemR23	90
fMLP	FPR	71
LL37	FPR2	130
F2L	FPR3	131
SAA	FPR2	59
C5a	C5aR	74
PAF	PAFR	81, 82
CRAMP	Fpr2	57
C1q	gC1qR, DC-SIGN	77, 132
PGE2	EP2, EP4	84
Plasmin	Akt2	80
LTB4	BLT1/2	31
CysLT	CysLT1	83
7α, 25-OHC	EBI2	86
S1P	S1PR1	87
Adenosine	P2YR, P2XR	78
	Epac1-Rap1	79
Activin A	ALK4, ActRIIA	58
HMGB1	RAGE	73
IL-18	IL-18R	97

Several observations underline the importance of lipid mediators in DC migration. Human and mouse DCs express functional receptors for the chemotactic lipid PAF[81,82]. Cysteinyl leukotrienes promote DC migration to lymph nodes in response to the CCR7 ligands CCL19 and CCL21[83]. Prostaglandin E2, acting through the EP2 and EP4 receptors, is a general mandatory factor for the development of migratory DCs in humans[84]. The LTB4/BLT1 axis is crucial in the regulation of DC trafficking and in the induction of adaptive immune responses[31]. In contrast, the lipid mediator Resolvin E1 inhibits cutaneous DC motility, possibly through the BLT1 receptor[85]. Some lipid chemotactic signals are implicated in homeostatic DC recruitment. The 7alpha,25-dihydroxycholesterol (7α,25-OHC), an oxysterol that binds the EBI2/GPR183 receptor, is required for the correct localization of a subset of splenic DCs, a necessary process for the activation of immune responses to particular antigens[86], whereas sphingosine-1 phosphate (S1P) regulates the localization of a subset of splenic immature DCs[87]. S1P is also involved in the regulation of DC migration in a model of skin contact hypersensitivity[88].

The role of several nonchemokine chemotactic proteins has been investigated. Chemerin, an antimicrobial peptide produced by epithelial cells and stromal cells, induces the in vitro and in vivo migration of DCs through the activation of the chemotactic

receptor CMKLR1[89]. Chemerin production was detected in the skin biopsies obtained from patients with autoimmune diseases such as systemic lupus erythematosus, lichen planus, and psoriasis and was correlated with myeloid and plasmacytoid DC tissue infiltration[90–94].

Some pleiotropic cytokines also regulate DC migration. Activin A, a member of the TGF-β family, induces the directional migration of immature DCs through the secondary release of chemokines, namely, CXCL12 and CXCL14[58,95]. In chronic diseases such as psoriasis and inflammatory bowel disease, the chemotactic activity of the proinflammatory cytokine IL-18 for human DC subsets was proposed as an additional mechanism for recruiting DCs to inflammatory areas characterized by a Th1 signature[96,97].

CONCLUDING REMARKS

DCs are professional antigen-presenting cells that bridge the innate and adaptive immune responses. After antigen capture, DCs leave peripheral tissues, enter the lymphatic system, and migrate to lymph nodes to localize in T-cell-rich areas. In the lymph nodes, DCs initiate adaptive responses by presenting antigens to specific T cells[1,2,4,5]. Although DCs specialize in the recognition and presentation of microbial-derived antigens, they are also activated by DAMPs, such as self-nucleic acids and present self-antigens. Therefore, DCs represent a key element in the activation of immunity versus tolerance. For this reason, DCs are implicated in a large variety of pathological conditions, including autoimmune diseases and cancers, and represent a valuable therapeutic target. Several DC-based antitumor vaccines are being tested on solid and hematological malignancies in clinical trials, and there are a number of studies focused on modulating DC migration to improve therapeutic responsiveness[98–100]. Blocking DC migration via the lymphatic system is under investigation as a therapeutic strategy for preventing transplant rejections[98,101,102].

The correct tissue localization is crucial for DC function. In PI3Kγ-deficient mice, defective signaling of the chemotactic receptors impairs specific immunity[18,103]. Therefore, chemokines and chemokine receptors represent a promising target for new therapeutic strategies focused on controlling DC activation. So far, only two drugs, acting as chemokine receptor antagonists, have reached the market. Maraviroc targets CCR5 for its role as a co-receptor for the cellular entry of the human immunodeficiency virus (HIV) and plerixafor targets CXCR4 for stem cell mobilization; a second CXCR4 receptor antagonist (X4P-001) is in phase II/III clinical trials[61]. No chemokine-targeting drug is currently available for inflammatory or autoimmune conditions.

Inflammation involves several amplification mechanisms that sustain the strength, the persistence, and the propagation of the response. Migrating leukocytes are simultaneously exposed to numerous stimuli and their response is the result of the integration of multiple pieces of information. These signals can converge to potentiate the response of already-migrating cells, or alternatively, the release of secondary chemokines that function as a signal relay mechanism.

The understanding of the mechanisms involved in the fine-tuning of DC migration, together with the new findings on the biology and functions of the emerging variety of DC subsets[104], are likely to uncover new potential pharmacological targets and represent a major future challenge.

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ADDITIONAL INFORMATION

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