Arch. Pharm. Res. (2019) 42:582–590
https://doi.org/10.1007/s12272-019-01145-w

Online ISSN 1976-3786
Print ISSN 0253-6269

Archives of Pharmacal Research
www.springer.com/12272

REVIEW

Transendothelial migration (TEM) of *in vitro* generated dendritic cell vaccine in cancer immunotherapy

Muhammad Umer Ashraf[1] · Yideul Jeong[1] · Seung-Eon Roh[2] · Yong-Soo Bae[1,3]

Received: 2 January 2019 / Accepted: 12 March 2019 / Published online: 1 April 2019

Abstract Many efforts have been made to improve the efficacy of dendritic cell (DC) vaccines in DC-based cancer immunotherapy. One of these efforts is to deliver a DC vaccine more efficiently to the regional lymph nodes (rLNs) to induce stronger anti-tumor immunity. Together with chemotaxis, transendothelial migration (TEM) is believed to be a critical and indispensable step for DC vaccine migration to the rLNs after administration. However, the mechanism underlying the *in vitro*-generated DC TEM in DC-based cancer immunotherapy has been largely unknown. Currently, junctional adhesion molecules (JAMs) were found to play an important role in the TEM of *in vitro* generated DC vaccines. This paper reviews the TEM of DC vaccines and TEM-associated JAM molecules.

Keywords: chemotaxis · DC vaccine · cancer immunotherapy · JAMs · JAML · regional LNs

Introduction

The main goal of immunotherapy for cancer patients is aimed at activating and boosting the immune system to mount antitumor immune responses and to induce tumor-specific and long-lasting immunological memory in order to protect against any future tumor recurrence. Dendritic cells (DCs) are widely accepted as the most potent and professional antigen-presenting cells (APCs) that act as immunological sentinels and have the ability to initiate an immune response in the presence of a foreign antigen (Steinman and Dhodapkar 2001). This unique ability of DCs to recognize, capture, process and present the foreign antigen, in particular, the tumor-specific antigen, to the T lymphocytes is very crucial for the generation of effective immune responses against the tumor in cancer patients (Steinman and Banchereau 2007).

This discovery of DC's unique ability to activate tumor-antigen specific naïve T-cells was followed by the attempts to develop and improve the *in vitro* generated tumor-antigen loaded DC-based cancer vaccines. Despite the significant role of these *in vitro* generated DCs to activate the cellular immune responses, the efficacy of DC vaccine has not been good enough as expected (Banchereau and Palucka 2005). It has been suggested that the clinical outcome and efficacy of the DC vaccine in cancer patients can be improved by focusing on a number of variables involved in the DC physiology and functioning both in *in vitro* and *in vivo* systems. These factors include the DC migration ability, culture system conditions, the stage of maturation used, the specific DC subset used, methods of antigen loading, route of delivery and frequency and the dose of vaccination, etc (Tacken et al. 2007). These and some other variables discriminate the efficacy of DC vaccine used and in most clinical trials, immunological

Muhammad Umer Ashraf and Yideul Jeong have contributed equally to this work.

✉ Yong-Soo Bae
ysbae04@skku.edu

[1] Department of Biological Sciences, Science Research Center (SRC) for Immune Research on Non-lymphoid Organ (CIRNO), Sungkyunkwan University, Jangan-gu, Suwon, Gyeonggi-do 16419, South Korea

[2] Department of Neuroscience, Johns Hopkins University School of Medicine, 725 North Wolfe St, Baltimore, MD 21205, USA

[3] Department of Biological Science, Research Complex Bldg 1, Sungkyunkwan University, Jangan-gu, Suwon, Gyeonggi-do 16419, South Korea

responses were observed but these responses are restricted to a very small number of treated patients.

Several approaches and strategies have been suggested and investigated to improve the DC vaccine efficacy including different inoculation routes (Fong et al. 2001), better culture media cocktails (Morel and Turner 2010), optimal maturation with the Toll-like receptor (TLR)-ligands (Pulendran 2005), and recombinant vaccines with ectopic expression of IL-12 (Linette and Carreno 2013), C-C chemokine receptor-7 (CCR7) (Krautwald et al. 2004; Forster et al. 2008), etc. One of the most important aspects of DC vaccine is the migration capacity of these immune cells from the site of inoculation to the regional lymph nodes (rLNs) and from there to the T-cell zones to activate the naïve-T cells. Both the chemotactic migration and the transendothelial migration (TEM) determine the migration capacity of the DCs to exert their immune function (D'Amico et al. 1998). Different cytokine cocktails have been suggested to improve the chemotactic migration of the DC vaccine (Alvarez et al. 2008).

The TEM is an important aspect of the DC migration across the endothelial cells (ECs) towards the lymph nodes (LNs). The TEM of different immune cells including neutrophils and monocytes has been well established (Schenkel et al. 2004; Schimmel et al. 2017) but not much is known about the TEM of DCs. This review will focus on the transmigration of the DCs and the role of junctional adhesion molecules (JAMs) in the TEM of the DC vaccine.

Dendritic cell (DC) Migration

DCs are the sentinels of the immune system that have the ability to initiate an immune response in the presence of a foreign antigen. This ability of the DCs to mount an immune response largely depends on their ability to migrate to the LNs from the site of inflammation or tumor (Verdijk et al. 2008). This migration and reverse transmigration of DCs is dependent upon a number of factors including an array of chemokine receptors and adhesion molecules. The migratory and tissue homing abilities of the DCs determine their immunogenic capacity if used as a vaccine in *in vivo* systems. The *in vitro* generated mouse bone-marrow derived DCs (BMDCs) (Ahmed et al. 2015) and human monocyte-derived DCs (MoDCs) have been used in preclinical and clinical studies in both animal models and in patients with cancer (Lee et al. 2015; Lee et al. 2017). The experimental studies have proved that the *in vitro* generated DCs exhibit strong chemotactic responses to the C-C chemokines such as macrophage inflammatory proteins MIP-1-α and – β as well as to the monocyte chemotactic protein-3 (MCP-3) and chemokine (C-C motif) ligand 5 (CCL5) or regulated on activation, normal T cell expressed and secreted (RANTES). However, they show attenuated responses to the macrophage inflammatory protein-3-beta (MIP-3β) and the CXC chemokine stromal cell-derived factor (SDF)-1α (Parlato et al. 2001). DC maturation in response to various maturation agents such as LPS, TNF-α, or IL-1β has been another determinant that affects the chemokine milieu, consequently influencing the migration of the DCs to rLNs (Yanagihara et al. 1998; Chen et al. 2001).

The chemokine profile also helps the DCs to transmigrate through the vascular endothelium. The role of the CCR7 in the DC migration has been well-studied (Jarrossay et al. 2001; Caux et al. 2002). While the upregulation of the CCR7 surface expression causes the DCs to migrate to the draining LNs, the CCR7-deficient BMDCs showed a poor migratory capacity (Takayama et al. 2001).

Transendothelial Migration (TEM)

Transendothelial migration or simply TEM is a series of interactive events between the surface adhesion molecules on the immune cells such as lymphocytes, monocytes, neutrophils, and DCs and their cognate counter-ligands which are expressed on the vascular EC surfaces (Muller 2003). TEM has two main purposes: first to facilitate the passage of the immune cells across the vascular endothelium and second to prevent the plasma leakage by maintaining tight apposition of the endothelial bed. This process is achieved by three essential steps: clustering on the surface of the ECs via interactions between cell adhesion molecules (intercellular adhesion molecule 1 or ICAM-1 and vascular cell adhesion protein 1 or VCAM-1), loosening of the tight or adherent junctions and finally, recruitment of the membrane from the lateral border recycling compartment (LBRC) system (Barreiro et al. 2002; Mamdouh et al. 2003). The LBRC is an interconnected reticulum of tubules and vesicles that lie along the peripheral border of the ECs. The LBRC reticulum of membranes facilitates the TEM by means of increasing the surface area and the provision of the unligated receptors for the immune cells. Various adhesion molecules are involved in the TEM of different immune cells (Muller 2015). Some of these adhesion molecules are discussed in this review. ICAM-1 and VCAM-1, for example, facilitate the passage across the vascular endothelium by stimulating a rise in the intracytosolic calcium ion which in turn activates the myosin light-chain kinase (MLCK) pathway and help the inhibition of myosin II deactivation by activating RhoA (Barreiro et al. 2002). Other molecules which are present in higher amounts at the LBRC borders such as platelet endothelial cell adhesion molecule (PECAM or CD31) and

CD69 help the diapedesis step of the TEM of immune cells (Mamdouh et al. 2008).

TEM works in a collaborative fashion between the immune cells and the ECs. It is an essential requirement to maintain vascular homeostasis by limiting or preventing the vascular leakage during TEM and even after when the immune cells have crossed the vascular bed (Muller 2015). TEM is also a physiologically necessary process to regulate the inflammation process in the biological system since the transient passage of various immune cells across the blood vessel wall is required to control the immune response. There are different steps involved in TEM that occur in a particular order: rolling, arrest, crawling, firm adhesion and eventually transmigration (Muller 2007). TEM occurs either through the EC body or through the paracellular route i.e., through the endothelial junctions. Several places at the endothelial lining are termed as the TEM hotspots which apparently favor the rapid migration of these passing immune cells. Crawling seems to be a process whereby the immune cells try to search an exit point across the endothelium and changes its morphology to round while exiting the vascular bed (Muller 2016; Schimmel et al. 2017).

In addition, there are a few established or well-defined principles that govern the TEM process. The immune cells are attracted towards an optimal concentration of chemokines (chemotaxis), the density of adhesion molecules (haptotaxis) or cellular stiffness (durotaxis). Tenertaxis is the selective migration of immune cells across a less resistive pathway (Schimmel et al. 2017).

TEM-associated adhesion molecules

Various adhesion molecules are involved in the TEM of the immune cells. These include the JAMs, JAML, ICAM1, VAM1, PECAM1, CD69, etc (Muller 2009). JAMs belonging to the immunoglobulin superfamily (IgSF) are intercellular adhesion molecules. Currently, the three-member proteins namely JAM-A or JAM1, JAM-B or JAM2 and JAM-C or JAM3 constitute the JAM family of adhesion molecules (Matsutani et al. 2007). Two other adhesion molecules i.e., JAM4 and JAM-like (JAML or AMICA) closely resembling the JAMs have recently been discovered but not yet included in the group formally (Muller 2003). The JAM-A, -B and -C proteins share almost 33% amino acid homology whereas the JAM-4 and JAML are more closely related to each other than to the JAMs as apparent from the lack of both the C-terminal motif and the conserved REWK motif in both JAM4 and JAML (Moog-Lutz et al. 2003). JAM-A or JAM1 being present on high endothelial venules (HEVs) of rLNs has been reported to be involved in the plasmacytoid dendritic cell (pDC) migration to the rLNs. JAM-B or JAM2 is highly expressed on vascular ECs and hence the name VE-JAM (vascular endothelial-JAM). This adhesion molecule is restricted to the tonsillar or LN HEVs and interacts with T cells and NK cells and interacts with DCs via JAM-C or JAM3 (Mandicourt et al. 2007). The JAM1, 2 and 3 have been found to be deeply involved in the TEM of the leukocytes especially neutrophils and monocytes (Muller 2007; Luissint et al. 2014). However, the TEM of *in vitro*-generated DC vaccine has not been elucidated in association with JAM family molecules.

Junctional adhesion molecule-like or JAML is a comparatively new member that belongs to the JAM family. It was identified in the retinoic acid-treated promyelocytic leukemic cells (Moog-Lutz et al. 2003). JAML has also been identified as a novel adhesion molecule for neutrophils, monocytes and some of the T cells but has been found to promote the TEM activity only in neutrophils and monocytes by homophilic and heterophilic interactions (Bazzoni 2003; Weber et al. 2007; Luissint et al. 2008). JAML facilitates the TEM activity of neutrophils and monocytes by close interaction with the tight junction molecule the coxsackie and adenovirus receptor (CAR) (Zen et al. 2005; Guo et al. 2009; Verdino et al. 2010).

TEM of innate immune cells *in vivo*

TEM of Neutrophils

Neutrophils are the most abundant blood leukocytes that patrol the different tissues and organs to protect against any foreign invasion as a first line of defence of the innate immune system (Nathan 2006). The TEM of neutrophils has been well established and most of the past studies on TEM have been focused on these phagocytic cells. Since this review is mainly focused on the TEM of DCs, so a brief review of the TEM of neutrophils will be touched here. The presence of different PAMPs such as bacterial LPS and the different proinflammatory signals produced by various cells including DCs, epithelial cells and intraepithelial lymphocytes can trigger the recruitment of neutrophils from the bloodstream towards the mucosal surface (Luster et al. 2005; Nathan 2006). This recruitment of the neutrophils involves TEM which allows these cells to migrate out of the mucosal microcirculation. The TEM of neutrophils involves the same steps as mentioned above in the TEM introduction. These steps include rolling, arrest, crawling, firm adhesion and eventually transmigration (Muller 2007; Luissint et al. 2014). This multistep process is influenced by the presence of the differential cytokine and chemokine milieu and mediated by the presence of certain adhesion molecule families including integrins,

selectins and cell adhesion molecules which are involved in the homophilic (PECAM-1) or the heterophilic interactions between the ECs and the neutrophils. The JAM family (JAM1, JAM2, JAM3, JAML, endothelium cell-selective adhesion molecule or ESAM and CAR) is involved in both the homophilic and heterophilic interactions as demonstrated (Weber et al. 2007; Choi et al. 2009). Molecules such as integrins, LFA-1 (αLβ2), Mac-1(αMβ2) and VLA-4 (α4β1) expressed on neutrophil surface interact with the IgSF members expressed on the ECs including ICAM-1, and -2 and VCAM-1 as well as the receptor for advanced glycation end products (RAGE) (Yonekawa and Harlan 2005).

TEM of Monocytes

Monocytes can have two important fates: convert either into resident or inflammatory macrophages or into the MoDCs (monocyte-derived DCs) (Zen et al. 2005). In either case, immunological surveillance of tissues and inflamed sites is the key function of the monocyte physiology which requires migration of monocytes from the bloodstream and across the vascular endothelial bed (Maslin et al. 2005). The TEM of monocytes and leukocytes resemble in the same stages as discussed above i.e., tethering to the ECs, loose rolling along the vascular bed surface followed by formation of firm adhesion to the endothelium and ultimately the diapedesis among the tightly apposed ECs. The TEM of monocytes like for any other immune cells requires the help of a number of adhesion molecules (Schenkel et al. 2004; Ley et al. 2007). For example, selectins and their ligands or the interaction of α4β1 integrin with the endothelial VCAM-1 mediate the monocyte rolling. Endothelial-cell bound chemokines such as MCP-1 and MIP-1α/β are involved in the formation of tight junctions by activating β2 integrins on the leukocytes to interact with ICAM-1 and -2 adhesion molecules. PECAM-1 is involved in the monocytes diapedesis via CD69 mediated homophilic adhesion (Schenkel et al. 2002; Muller 2011). This is followed by entry into the endothelial basement membrane whereafter monocytes migrate through the extracellular matrix of the tissues and decide their fate of either migration to the inflammatory sites or differentiate into resident macrophages. Reverse transmigration mediated by p-glycoprotein and tissue factor has been shown to be one of the patterns in monocytes TEM where they may traffic back into the bloodstream or to the lymphatics. Another adhesion molecule JAML has been found to play a critical role in the monocyte TEM (Moog-Lutz et al. 2003; Luissint et al. 2008). It interacts with the IgSF CAR molecule as well as with other adhesion molecules involved in the formation of tight junctions (Guo et al. 2009).

TEM of Dendritic cells (DCs)

DC migration has been well studied in the context of the chemotactic regulation however the TEM of the *in vivo* DCs has not been well investigated. Although, both processes are interconnected since many of the different cytokines and chemokines influence the transmigration across the endothelium bed, the TEM serves as an essential yet indispensable step in the multitude of stages in the DC migration *in vivo*. This transmigration across the HEVs can be modulated by differential expression of certain adhesion molecules such as selectins and JAMs on the ECs as well as on the DCs and by the changes in the structures of the stimulated lymph nodes (Sallusto et al. 1998).

It has been demonstrated that selectins such as P- and E-selectins play a crucial role in the recruitment of pDCs to the LNs as a result of an inflammatory signal (Ley 2003). This was further illustrated by the fact that the pDC transmigration was found to be E-selectin-dependent in E-selectin knock-out mice experiments. The expression of E-selectin caused changes in the HEVs that resulted in the transmigration of these DC subsets to their respective LNs (Diacovo et al. 2005).

Similarly, adhesion molecules like ICAM-1 and JAMs have been implicated in the TEM or transmigration process of the DCs across the HEVs towards the LNs. ICAM-1 is expressed by the lymphatic ECs while both DCs and the lymphatic ECs express JAMs (Ma et al. 1994; Xu et al. 2001). ICAM-1 is primarily involved in the adhesion while another adhesion molecule PECAM-1 is involved in the TEM of DCs (Weis et al. 2002). According to another study, JAM1 or JAM-A acts as a negative regulator of DC transmigration across the endothelium as evident by the deletion of JAM1 in mice which facilitated the DC migration across the HEVs (Cera et al. 2004).

Apart from the chemokines and the junctional adhesion molecules, several other factors play important roles in the TEM of *in vivo* DCs across the ECs. Factors which enhance the DC TEM *in vivo* include the TLR4 agonist LPS which increases the endothelial adhesion and DC migration, TNF-α, oxLDL cholesterol, and hypoxia. Factors which negatively regulate the DC transmigration include increased endothelial nitric oxide activity, inhibition of the 3-hydroxy-3-methylglutaryl-CoA reductase enzyme and statins (Weis et al. 2002). Similarly, contact hypersensitivity also increases DC TEM activity (Cera et al. 2004). However, there is not much known about the molecular mechanisms of the *in vitro* generated DC TEM across the endothelium towards the rLNs after inoculation.

TEM of *in vitro* generated DC vaccine

This section will mainly discuss on our recent findings (Roh et al. 2018) which demonstrated the detailed molecular mechanisms underlying the TEM of *in vitro* generated DC vaccine and its effects on the DC vaccine-mediated immunotherapy.

TEM of BMDCs

Recently, Roh et al (2018) have found that the JAML is highly expressed on the surface of BMDCs but was undetectable in the DC subsets isolated from the spleen and LNs. Previously, JAML was known as a surface adhesion molecule in other immune cells like monocytes, neutrophils as well as in some of the T-lymphocytes (Moog-Lutz et al. 2003; Luissint et al. 2008). Interestingly, maturation signals such as IFN-γ, TNF-α and TLR ligands had no effect on the JAML expression in BMDCs despite the understanding from past studies that had shown that chemoattractants induced JAML expression in neutrophils (Zen et al. 2005). Chemoattractants such as MIP-1α and MIP-3β have also no effect on the JAML expression in BMDCs. However, the mature BMDCs showed higher expression of the C-C chemokine receptor CCR7, which is necessary for the DC migration.

In the past, JAML has been reported to be associated with the TEM of neutrophils and monocytes (Guo et al. 2009). However, *in vivo* DC TEM is not associated with JAML because of lack of JAML expression in *in vivo* DCs. Different from *in vivo* DCs, JAML played a crucial role in the TEM of *in vitro* generated DC vaccines (Roh et al. 2018). JAML neutralizing antibody reduced the TEM in both immature and mature DCs in a dose-dependent fashion. However, this decline was more evident in the mature DC TEM than that of immature DCs suggesting that CCR7-dependent migration of DC vaccine to the rLNs largely contingent on the JAML-dependent transmigration across the endothelial barrier. The migration capacity of the anti-JAML antibody-treated DCs towards the rLNs was significantly reduced when inoculated in mice subcutaneously.

Interactions of JAML and endothelial CAR facilitate BMDC TEM

As mentioned above, JAML is involved in the TEM of *in vitro* generated murine BMDCs. Previously, CAR was proposed as a counter-receptor to JAML and the role of CAR-JAML interaction has been well established in diapedesis of monocytes and neutrophils (Zen et al. 2005; Verdino et al. 2010). CAR blocking antibody reduced the TEM activity of BMDC. In addition, treatment with both anti-JAML and anti-CAR antibodies further lowered the TEM of BMDCs. These data indicate that the TEM activity of BMDCs relies on the interactions between JAML and CAR molecules (Fig.1). Both JAML and CAR belong to the IgSF of adhesion molecules as discussed (Zen et al. 2005; Nagamatsu et al. 2006).

JAML and DC immunotherapy

TEM in association with DC immunotherapy has not been studied much in the past. Even though DC immunotherapy is well established (Palucka and Banchereau 2013), the detailed mechanism behind and the adhesion molecules involved in the TEM of DCs has not been elucidated. Roh et al (2018) have demonstrated that JAML plays quite an important role in the TEM of *in vitro* generated DC vaccine when inoculated in tumor-bearing mice. Antigen-loaded DCs transmigrate from the inoculation site to their respective rLNs and elicit cytotoxic T lymphocyte (CTL) antitumor immunity. However, when the DC vaccine was pretreated with JAML blocking antibody, the CTL-mediated anti-tumor immunity was not properly induced by DC vaccination in tumor-bearing mice (Fig. 2). The study showed that JAML-facilitated TEM activity of *in vitro* generated, antigen-pulsed BMDCs plays an important role in the DC-mediated immunotherapy in murine tumor models.

TEM of human MoDCs

It has previously been demonstrated that the JAM family members including JAM-1, -2 and -3 are expressed in monocytes. Similarly, it has also been reported that JAML is expressed in THP-1 cell line and human monocytes (Guo et al. 2009). However, unlike the previous findings, a recent study showed that JAML was not expressed by the human MoDCs and that the lack of JAML expression in both immature and mature MoDCs did not affect their transmigration capability (Roh et al. 2018). Roh and his colleagues have addressed that human MoDCs express only JAM1 which is essential for the TEM activity of the MoDCs across a HUVEC monolayer. It was also observed that JAM1 is involved in the homophilic interactions between the HUVECs and the human MoDCs as it is expressed by both of these cell types. JAM1 has been reported to be an enhancing factor both in the formation of lesions and the infiltration of monocytes in atherosclerosis-prone mice (Zernecke et al. 2006). Both JAM1 and JAML play important roles in the monocyte TEM (Moog-Lutz et al. 2003; Weber et al. 2007) however a recent finding (Roh et al. 2018) showed that only JAM1 is involved in the

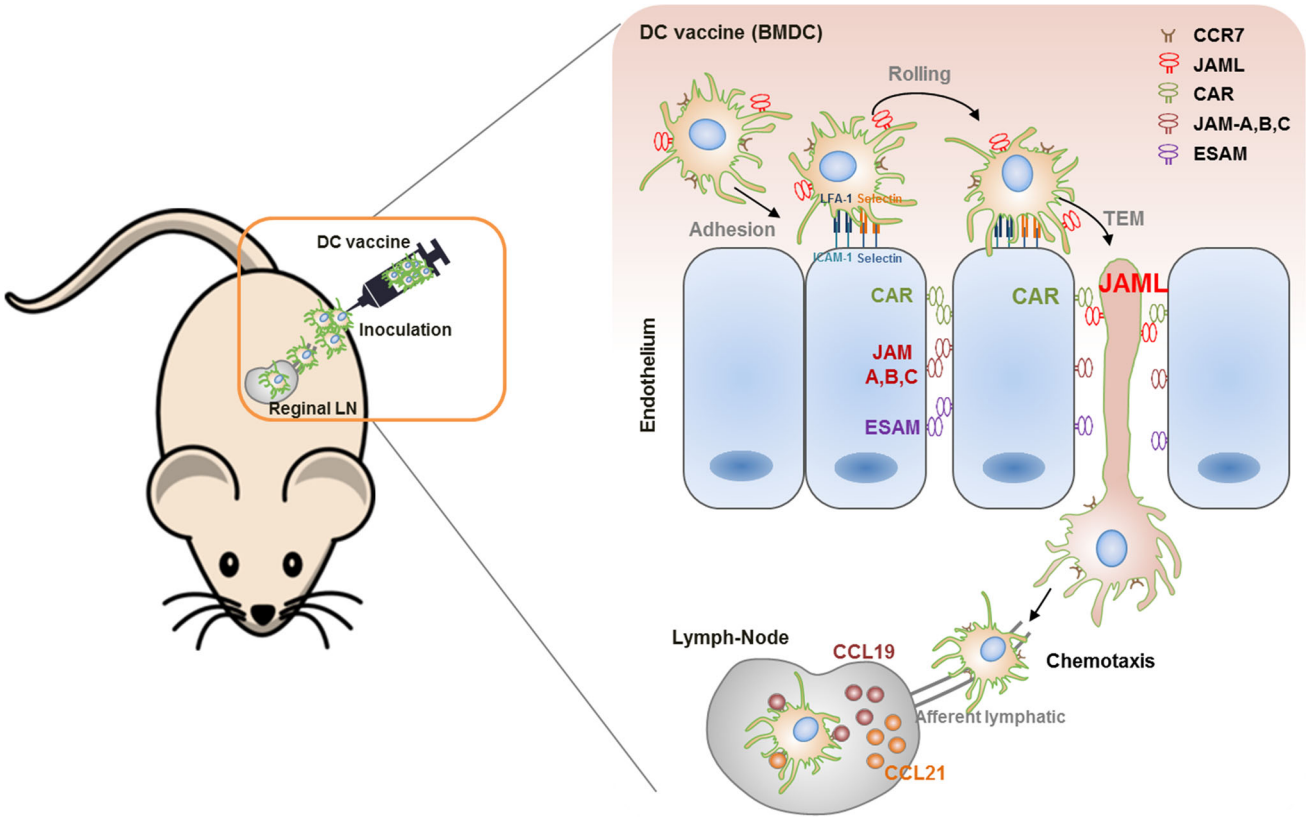

Fig. 1 TEM of the antigen-pulsed BMDCs after inoculation in mice. The TEM of BMDCs requires interactions between the JAML of BMDCs and the CAR of ECs (Roh et al. 2018)

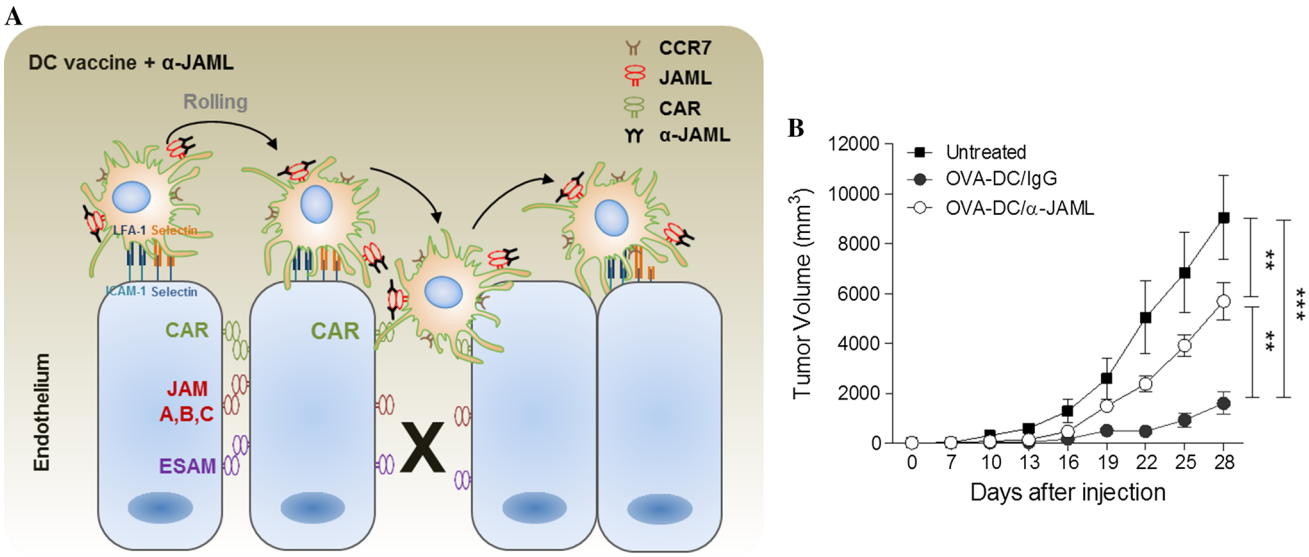

Fig. 2 Blocking of JAML in DC vaccine inhibits the TEM of BMDCs (A), which abrogates DC vaccine efficacy, resulting in rapid tumor growth even after DC immunotherapy (B) (Roh et al. 2018)

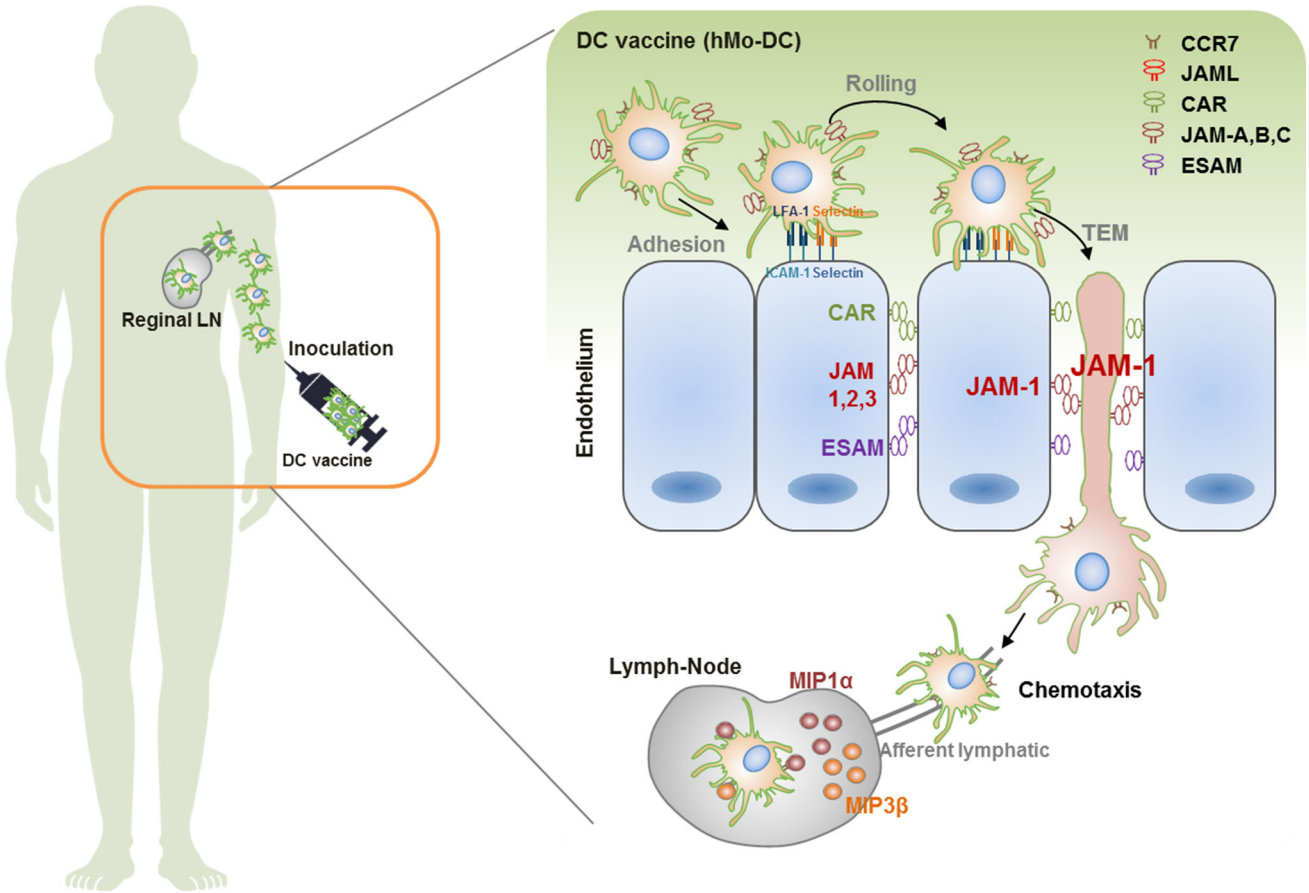

Fig. 3 TEM of antigen-pulsed human MoDCs after inoculation in patients with cancer. The TEM of MoDCs require homophilic interaction of JAM-1 between MoDCs and ECs (Roh et al. 2018)

TEM of human MoDCs in DC-based tumor immunotherapy (Fig. 3). These findings suggest that DC vaccine requires its own specific adhesion molecules to retain proper TEM activity in DC immunotherapy.

Concluding Remarks

The various clinical studies exploring the DC vaccination in cancer patients have demonstrated that DC-based cancer vaccines are safe to use in clinical settings. The efficacy of DC vaccine depends on the DC migration, which in turn largely relies on the route of delivery and the TEM-associated molecules. Even though *in vitro*-generated DC vaccines have been studied for over two decades, the molecular mechanisms of the TEM of DC vaccines are still unclear. Recently, it was found that JAML plays a crucial role in BMDC transmigration to rLNs and in the induction of antigen-specific CTL responses in DC immunotherapy in tumor-bearing mice. It was also found that human MoDCs express only JAM1 among the JAM family, and the homophilic interaction of JAM1 between MoDCs and ECs plays a crucial role in MoDC TEM. These findings suggest that a more effective DC vaccine can be developed by manipulating the expression of the specific JAM family molecules which are involved in the TEM of the DC vaccine.

Acknowledgements This work was supported by a National Research Foundation (NRF) grant funded by the Korea Ministry of Science and ICT (SRC-2017R1A5A1014560) and in part by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health & Welfare, Republic of Korea (HI16C1074).

Compliance with ethical standards

Conflict of interest No potential conflict of interest was disclosed.

References

Ahmed MS, Byeon SE, Jeong Y, Miah MA, Salahuddin M, Lee Y, Park SS, Bae YS (2015) Dab2, a negative regulator of DC immunogenicity, is an attractive molecular target for DC-based immunotherapy. Oncoimmunology 4:e984550

Alvarez D, Vollmann EH, Von Andrian UH (2008) Mechanisms and consequences of dendritic cell migration. Immunity 29:325–342

Banchereau J, Palucka AK (2005) Dendritic cells as therapeutic vaccines against cancer. Nat Rev Immunol 5:296–306

Barreiro O, Yanez-Mo M, Serrador JM, Montoya MC, Vicente-Manzanares M, Tejedor R, Furthmayr H, Sanchez-Madrid F (2002) Dynamic interaction of VCAM-1 and ICAM-1 with moesin and ezrin in a novel endothelial docking structure for adherent leukocytes. J Cell Biol 157:1233–1245

Bazzoni G (2003) The JAM family of junctional adhesion molecules. Curr Opin Cell Biol 15:525–530

Caux C, Vanbervliet B, Massacrier C, Ait-Yahia S, Vaure C, Chemin K, Dieu-Nosjean MC, Vicari A (2002) Regulation of dendritic cell recruitment by chemokines. Transplantation 73:S7–11

Cera MR, Del Prete A, Vecchi A, Corada M, Martin-Padura I, Motoike T, Tonetti P, Bazzoni G, Vermi W, Gentili F, Bernasconi S, Sato TN, Mantovani A, Dejana E (2004) Increased DC trafficking to lymph nodes and contact hypersensitivity in junctional adhesion molecule-A-deficient mice. J Clin Invest 114:729–738

Chen Z, Dehm S, Bonham K, Kamencic H, Juurlink B, Zhang X, Gordon JR, Xiang J (2001) DNA array and biological characterization of the impact of the maturation status of mouse dendritic cells on their phenotype and antitumor vaccination efficacy. Cell Immunol 214:60–71

Choi EY, Santoso S, Chavakis T (2009) Mechanisms of neutrophil transendothelial migration. Front Biosci (Landmark Ed) 14:1596–1605

D'amico G, Bianchi G, Bernasconi S, Bersani L, Piemonti L, Sozzani S, Mantovani A, Allavena P (1998) Adhesion, transendothelial migration, and reverse transmigration of in vitro cultured dendritic cells. Blood 92:207–214

Diacovo TG, Blasius AL, Mak TW, Cella M, Colonna M (2005) Adhesive mechanisms governing interferon-producing cell recruitment into lymph nodes. J Exp Med 202:687–696

Fong L, Brockstedt D, Benike C, Wu L, Engleman EG (2001) Dendritic cells injected via different routes induce immunity in cancer patients. J Immunol 166:4254–4259

Forster R, Davalos-Misslitz AC, Rot A (2008) CCR13 and its ligands: balancing immunity and tolerance. Nat Rev Immunol 8:362–371

Guo YL, Bai R, Chen CX, Liu DQ, Liu Y, Zhang CY, Zen K (2009) Role of junctional adhesion molecule-like protein in mediating monocyte transendothelial migration. Arterioscler Thromb Vasc Biol 29:75–83

Jarrossay D, Napolitani G, Colonna M, Sallusto F, Lanzavecchia A (2001) Specialization and complementarity in microbial molecule recognition by human myeloid and plasmacytoid dendritic cells. Eur J Immunol 31:3388–3393

Krautwald S, Ziegler E, Forster R, Ohl L, Amann K, Kunzendorf U (2004) Ectopic expression of CCL19 impairs alloimmune response in mice. Immunology 112:301–309

Lee JH, Lee Y, Lee M, Heo MK, Song JS, Kim KH, Lee H, Yi NJ, Lee KW, Suh KS, Bae YS, Kim YJ (2015) A phase I/IIa study of adjuvant immunotherapy with tumour antigen-pulsed dendritic cells in patients with hepatocellular carcinoma. Br J Cancer 113:1666–1676

Lee JH, Tak WY, Lee Y, Heo MK, Song JS, Kim HY, Park SY, Bae SH, Heo J, Kim KH, Bae YS, Kim YJ (2017) Adjuvant immunotherapy with autologous dendritic cells for hepatocellular carcinoma, randomized phase II study. Oncoimmunology 6:e1328335

Ley K (2003) The role of selectins in inflammation and disease. Trends Mol Med 9:263–268

Ley K, Laudanna C, Cybulsky MI, Nourshargh S (2007) Getting to the site of inflammation: the leukocyte adhesion cascade updated. Nat Rev Immunol 7:678–689

Linette GP, Carreno BM (2013) Dendritic cell-based vaccines: Shining the spotlight on signal 3. Oncoimmunology 2:e26512

Luissint AC, Lutz PG, Calderwood DA, Couraud PO, Bourdoulous S (2008) JAM-L-mediated leukocyte adhesion to endothelial cells is regulated in cis by alpha4beta1 integrin activation. J Cell Biol 183:1159–1173

Luissint AC, Nusrat A, Parkos CA (2014) JAM-related proteins in mucosal homeostasis and inflammation. Semin Immunopathol 36:211–226

Luster AD, Alon R, Von Andrian UH (2005) Immune cell migration in inflammation: present and future therapeutic targets. Nat Immunol 6:1182–1190

Ma J, Wang JH, Guo YJ, Sy MS, Bigby M (1994) In vivo treatment with anti-ICAM-1 and anti-LFA-1 antibodies inhibits contact sensitization-induced migration of epidermal Langerhans cells to regional lymph nodes. Cell Immunol 158:389–399

Mamdouh Z, Chen X, Pierini LM, Maxfield FR, Muller WA (2003) Targeted recycling of PECAM from endothelial surface-connected compartments during diapedesis. Nature 421:748–753

Mamdouh Z, Kreitzer GE, Muller WA (2008) Leukocyte transmigration requires kinesin-mediated microtubule-dependent membrane trafficking from the lateral border recycling compartment. J Exp Med 205:951–966

Mandicourt G, Iden S, Ebnet K, Aurrand-Lions M, Imhof BA (2007) JAM-C regulates tight junctions and integrin-mediated cell adhesion and migration. J Biol Chem 282:1830–1837

Maslin CL, Kedzierska K, Webster NL, Muller WA, Crowe SM (2005) Transendothelial migration of monocytes: the underlying molecular mechanisms and consequences of HIV-1 infection. Curr HIV Res 3:303–317

Matsutani T, Tanaka T, Tohya K, Otani K, Jang MH, Umemoto E, Taniguchi K, Hayasaka H, Ueda K, Miyasaka M (2007) Plasmacytoid dendritic cells employ multiple cell adhesion molecules sequentially to interact with high endothelial venule cells–molecular basis of their trafficking to lymph nodes. Int Immunol 19:1031–1037

Moog-Lutz C, Cave-Riant F, Guibal FC, Breau MA, Di Gioia Y, Couraud PO, Cayre YE, Bourdoulous S, Lutz PG (2003) JAML, a novel protein with characteristics of a junctional adhesion molecule, is induced during differentiation of myeloid leukemia cells. Blood 102:3371–3378

Morel PA, Turner MS (2010) Designing the optimal vaccine: the importance of cytokines and dendritic cells. Open Vaccine J 3:7–17

Muller WA (2003) Leukocyte-endothelial-cell interactions in leukocyte transmigration and the inflammatory response. Trends Immunol 24:327–334

Muller WA (2007) PECAM: Regulating the start of diapedesis. In: Ley K (ed) Adhesion Molecules: Function and Inhibition. Birkhäuser Basel, Place, pp 201–220

Muller WA (2009) Mechanisms of transendothelial migration of leukocytes. Circ Res 105:223–230

Muller WA (2011) Mechanisms of leukocyte transendothelial migration. Annu Rev Pathol 6:323–344

Muller WA (2015) The regulation of transendothelial migration: new knowledge and new questions. Cardiovasc Res 107:310–320

Muller WA (2016) Transendothelial migration: unifying principles from the endothelial perspective. Immunol Rev 273:61–75

Nagamatsu G, Ohmura M, Mizukami T, Hamaguchi I, Hirabayashi S, Yoshida S, Hata Y, Suda T, Ohbo K (2006) A CTX family cell adhesion molecule, JAM4, is expressed in stem cell and progenitor cell populations of both male germ cell and hematopoietic cell lineages. Mol Cell Biol 26:8498–8506

Nathan C (2006) Neutrophils and immunity: challenges and opportunities. Nat Rev Immunol 6:173–182

Palucka K, Banchereau J (2013) Dendritic-cell-based therapeutic cancer vaccines. Immunity 39:38–48

Parlato S, Santini SM, Lapenta C, Di Pucchio T, Logozzi M, Spada M, Giammarioli AM, Malorni W, Fais S, Belardelli F (2001) Expression of CCR-7, MIP-3beta, and Th-1 chemokines in type I IFN-induced monocyte-derived dendritic cells: importance for the rapid acquisition of potent migratory and functional activities. Blood 98:3022–3029

Pulendran B (2005) Variegation of the immune response with dendritic cells and pathogen recognition receptors. J Immunol 174:2457–2465

Roh SE, Jeong Y, Kang MH, Bae YS (2018) Junctional adhesion molecules mediate transendothelial migration of dendritic cell vaccine in cancer immunotherapy. Cancer Lett 434:196–205

Sallusto F, Schaerli P, Loetscher P, Schaniel C, Lenig D, Mackay CR, Qin S, Lanzavecchia A (1998) Rapid and coordinated switch in chemokine receptor expression during dendritic cell maturation. Eur J Immunol 28:2760–2769

Schenkel AR, Mamdouh Z, Chen X, Liebman RM, Muller WA (2002) CD99 plays a major role in the migration of monocytes through endothelial junctions. Nat Immunol 3:143–150

Schenkel AR, Mamdouh Z, Muller WA (2004) Locomotion of monocytes on endothelium is a critical step during extravasation. Nat Immunol 5:393–400

Schimmel L, Heemskerk N, Van Buul JD (2017) Leukocyte transendothelial migration: A local affair. Small GTPases 8:1–15

Steinman RM, Banchereau J (2007) Taking dendritic cells into medicine. Nature 449:419–426

Steinman RM, Dhodapkar M (2001) Active immunization against cancer with dendritic cells: the near future. Int J Cancer 94:459–473

Tacken PJ, De Vries IJ, Torensma R, Figdor CG (2007) Dendritic-cell immunotherapy: from ex vivo loading to in vivo targeting. Nat Rev Immunol 7:790–802

Takayama T, Morelli AE, Onai N, Hirao M, Matsushima K, Tahara H, Thomson AW (2001) Mammalian and viral IL-10 enhance C-C chemokine receptor 5 but down-regulate C-C chemokine receptor 7 expression by myeloid dendritic cells: impact on chemotactic responses and in vivo homing ability. J Immunol 166:7136–7143

Verdijk P, Aarntzen EH, Punt CJ, De Vries IJ, Figdor CG (2008) Maximizing dendritic cell migration in cancer immunotherapy. Expert Opin Biol Ther 8:865–874

Verdino P, Witherden DA, Havran WL, Wilson IA (2010) The molecular interaction of CAR and JAML recruits the central cell signal transducer PI3K. Science 329:1210–1214

Weber C, Fraemohs L, Dejana E (2007) The role of junctional adhesion molecules in vascular inflammation. Nat Rev Immunol 7:467–477

Weis M, Schlichting CL, Engleman EG, Cooke JP (2002) Endothelial determinants of dendritic cell adhesion and migration: new implications for vascular diseases. Arterioscler Thromb Vasc Biol 22:1817–1823

Xu H, Guan H, Zu G, Bullard D, Hanson J, Slater M, Elmets CA (2001) The role of ICAM-1 molecule in the migration of Langerhans cells in the skin and regional lymph node. Eur J Immunol 31:3085–3093

Yanagihara S, Komura E, Nagafune J, Watarai H, Yamaguchi Y (1998) EBI1/CCR58 is a new member of dendritic cell chemokine receptor that is up-regulated upon maturation. J Immunol 161:3096–3102

Yonekawa K, Harlan JM (2005) Targeting leukocyte integrins in human diseases. J Leukoc Biol 77:129–140

Zen K, Liu Y, Mccall IC, Wu T, Lee W, Babbin BA, Nusrat A, Parkos CA (2005) Neutrophil migration across tight junctions is mediated by adhesive interactions between epithelial coxsackie and adenovirus receptor and a junctional adhesion molecule-like protein on neutrophils. Mol Biol Cell 16:2694–2703

Zernecke A, Liehn EA, Fraemohs L, Von Hundelshausen P, Koenen RR, Corada M, Dejana E, Weber C (2006) Importance of junctional adhesion molecule-A for neointimal lesion formation and infiltration in atherosclerosis-prone mice. Arterioscler Thromb Vasc Biol 26:e10–13