OncoImmunology 3, e27897; January 2014; © 2014 Landes Bioscience

Drag cells in immunity

Plasmacytoid DCs dress up as cancer cells

Irene Bonaccorsi[1,2], Gaetana Pezzino[1,2], Barbara Morandi[3], and Guido Ferlazzo[1,2,*]

[1]Laboratory of Immunology and Biotherapy; Department of Human Pathology; University of Messina; Messina, Italy; [2]Cell Therapy Program; A.O.U. Policlinico "G.Martino"; Messina, Italy; [3]Department of Experimental Medicine (DIMES); University of Genoa; Genoa, Italy

Keywords: antigen presentation, CD8⁺ T lymphocytes, cross-dressing, HLA, interferon γ, phagocytosis, plasmacytoid dendritic cells, trogocytosis, tumor-associated antigens

Cross-dressing, in immunology, is a term originally coined to indicate the transfer of peptide-MHC complexes belonging to neighboring cells on antigen presenting cells. We have recently shown that plasmacytoid dendritic cells (pDCs) are particularly suited to be cross-dressed by tumor cells and that this phenomenon provides a unique pathway for abundant presentation of tumor antigens by pDCs.

Dendritic cells (DCs) are a peculiar type of highly efficient antigen-presenting cells (APCs) that plays a fundamental role in the initiation and modulation of immune responses. The existence of the DC system is critical for tumor immunology, as the initiation of T cell-mediated immune responses against tumor-associated antigens (TAAs) is particularly demanding.

To drive the generation of cytotoxic cells that are able to eliminate cancer cells, DCs are supposed to present TAA-derived peptides complexed with MHC class I molecules to CD8⁺ cytotoxic T lymphocytes (CTLs). A feature that renders DCs highly efficient as APCs is their ability to engage in cross-presentation, that is, to present exogenous antigens not only on MHC class II but also on MHC class I molecules. This said, not all DC subsets are equally proficient at cross-presentation.[1] Thus, while human DCs expressing thrombomodulin (THBD, best known as BDCA3) and C-type lectin domain family 9, member A (CLEC9A) are highly efficient at cross-presentation, in particular when soluble antigens are involved, plasmacytoid dendritic cells (pDCs) appear to be near-to-completely devoid of this capacity.[2]

Recently, a different mechanism involving the direct transfer of MHC-peptide complexes between cell membranes has been suggested to underlie the MHC class I-restricted presentation of antigenic determinants (including TAAs) by DCs.[3] This process, potentially resulting in the priming of CD8⁺ T cells, has been named "DC cross-dressing."[4] Although cross-dressing has been extensively documented in conventional myeloid DCs (mDCs), until recently it remained unclear whether this phenomenon also involves pDCs.

pDCs are a subset of DCs well known for their ability to produce large amounts of type I interferon (IFN) upon stimulation with Toll-like receptor (TLR) agonists. However, some aspects of the biology of pDCs, including the mechanisms whereby they present exogenous antigens, are still a matter of debate. Many of these controversies originated from divergent reports on the phagocytic competence of pDCs, although it is generally accepted that pDCs are less proficient at engulfing exogenous material than conventional mDCs. These unresolved issues hampered our understanding of the role of pDCs in the presentation of TAAs, especially MHC class I-restricted TAAs.

We have recently identified a new pathway by which pDCs can potentially present large amount of TAAs despite their reduced phagocytic potential.[5] In this setting, we confirmed that pDCs are unable to engulf particulate material including cell debris and bacteria, but are particularly proficient at acquiring cell membrane patches from neighboring cancer cells. Such a transfer of membrane patches occurs in a very short interval of time and closely resembles "trogocytosis," i.e., the exchange of cellular components upon cell-to-cell contact, a phenomenon that is well-documented in several biological systems.

Of note, the exchange of cell membrane patches occurring between neoplastic cells and pDCs results in the transfer of TAAs complexed with MHC class I molecules. These complexes persist on the surface of cross-dressed pDCs for up to 48 h and can therefore be efficiently recognized by tumor-specific CTLs. Remarkably, the cross-dressing of pDCs occurs upon contact with malignant cells of different histotypes and can also occur in vivo, as demonstrated by the presence of TAAs on the surface of pDCs isolated from human colorectal carcinomas.[5] These observations obviously raise questions about the functional consequences of TAA presentation by cross-dressed pDCs in the

*Correspondence to: Guido Ferlazzo; Email: guido.ferlazzo@unime.it
Submitted: 02/05/2014; Accepted: 02/10/2014; Published Online: 03/07/2014
Citation: Bonaccorsi I, Pezzino G, Morandi B, Ferlazzo G. Drag cells in immunity: plasmacytoid DCs dress up as cancer cells. OncoImmunology 2014; 3:e28184; http://dx.doi.org/10.4161/onci.28184

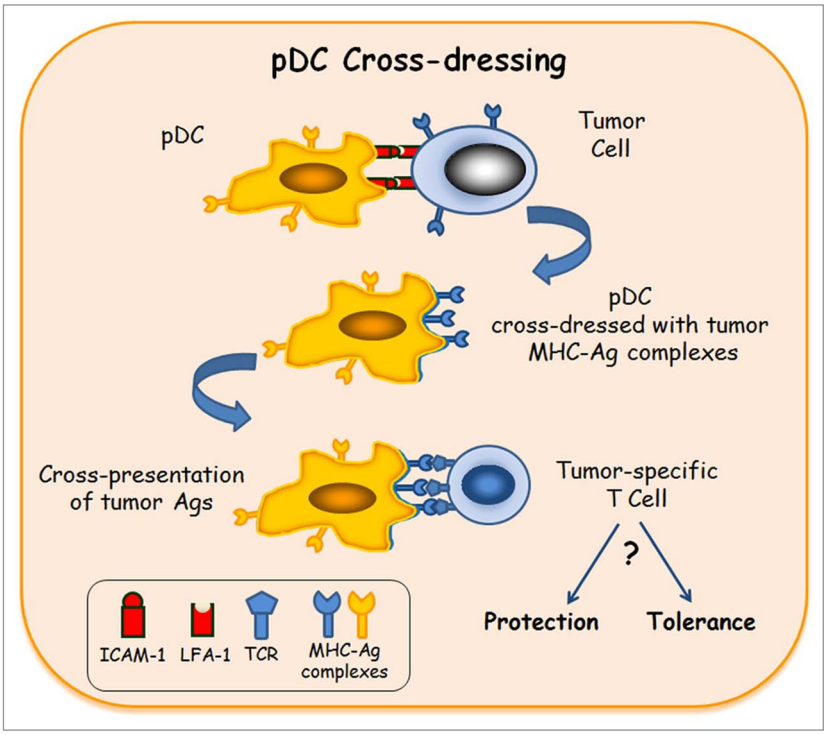

Figure 1. Plasmacytoid dendritic cells can present tumor-associated antigens to T lymphocytes by cross-dressing. Plasmacytoid dendritic cells (pDCs) are particularly proficient at acquiring cell membrane patches from neighboring cancer cells via a mechanism that requires cell-to-cell contacts and involves adhesion molecules. Such a transfer results in the cross-dressing of pDCs with MHC complexes bearing tumor-associated antigens, which can be efficiently recognized by tumor-specific T lymphocytes. The fate of T cells cross-primed by cross-dressed pDCs and the factors that determine it remain to be fully elucidated.

context of antitumor immune responses (**Fig. 1**).

pDCs have been involved in the maintenance of both central and peripheral tolerance,[6,7] the latter via the induction of regulatory T cells. This would explain the negative correlation between pDC infiltration and prognosis in patients affected by different neoplasms.[8] However, there is a general consensus around the notion that pDCs can promote immune activation, rather than tolerance, depending on maturation stage, although the precise factors determining the fate of T cells primed by pDCs remain to be elucidated. This scenario is particularly intriguing considering that pDCs have recently been identified in the afferent skin lymph of sheep and mini-pigs,[9] implying that pDCs, similarly to their myeloid counterparts,[10] can leave peripheral tissues and migrate to secondary lymphoid organs with their antigenic load. As the migration of pDCs via the afferent lymph has been documented even in steady-state conditions,[9] this mechanism may underlie the implication of pDCs in the maintenance of tolerance toward self antigens. Thus, upon emigration from neoplastic lesions tissues, pDCs may promote the anergy of tumor-specific T cells. However, pDCs do not necessarily need to reach locoregional lymph nodes for the presentation of cross-dressed antigens, as they might promote tolerance within neoplastic lesions by impairing the functions of local tumor-specific T cells.

Thus, further studies aimed at shedding some light on the factors that determine the functional outcome of antigen presentation by pDCs, i.e., activation or tolerization of T lymphocytes, are urgently needed. Given that pDCs cross-dressed with TAA in complex with MHC class I molecules maintained most of their peculiar features, including the ability to produce large amounts of type I IFN following stimulation with TLR9 agonists, interventions designed to activate intratumoral pDCs might offer a useful immunotherapeutic tool against cancer. This strategy might allow not only for the amplification of innate antitumor immune responses through the release of type I IFN but also for the avoidance of possible tolerogenic effects through the induction of pDC maturation, thus exploiting this "transvestism" attitude of pDCs for boosting tumor-specific adaptive immune responses.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Segura E, Amigorena S. Cross-presentation by human dendritic cell subsets. Immunol Lett 2013; 158:73-8; PMID:24333339; http://dx.doi.org/10.1016/j.imlet.2013.12.001
2. Salio M, Palmowski MJ, Atzberger A, Hermans IF, Cerundolo V. CpG-matured murine plasmacytoid dendritic cells are capable of in vivo priming of functional CD8 T cell responses to endogenous but not exogenous antigens. J Exp Med 2004; 199:567-79; PMID:14970182; http://dx.doi.org/10.1084/jem.20031059
3. Dolan BP, Gibbs KD Jr., Ostrand-Rosenberg S. Dendritic cells cross-dressed with peptide MHC class I complexes prime CD8+ T cells. J Immunol 2006; 177:6018-24; PMID:17056526
4. Yewdell JW, Haeryfar SM. Understanding presentation of viral antigens to CD8+ T cells in vivo: the key to rational vaccine design. Annu Rev Immunol 2005; 23:651-82; PMID:15771583; http://dx.doi.org/10.1146/annurev.immunol.23.021704.115702
5. Bonaccorsi I, Morandi B, Antsiferova O, Costa G, Oliveri D, Conte R, Pezzino G, Vermiglio G, Anastasi GP, Navarra G, et al. Membrane transfer from tumor cells overcomes deficient phagocytic ability of plasmacytoid dendritic cells for the acquisition and presentation of tumor antigens. J Immunol 2014; 192:824-32; PMID:24337377; http://dx.doi.org/10.4049/jimmunol.1301039
6. Hadeiba H, Lahl K, Edalati A, Oderup C, Habtezion A, Pachynski R, Nguyen L, Ghodsi A, Adler S, Butcher EC. Plasmacytoid dendritic cells transport peripheral antigens to the thymus to promote central tolerance. Immunity 2012; 36:438-50; PMID:22444632; http://dx.doi.org/10.1016/j.immuni.2012.01.017
7. Gilliet M, Liu YJ. Human plasmacytoid-derived dendritic cells and the induction of T-regulatory cells. Hum Immunol 2002; 63:1149-55; PMID:12480258; http://dx.doi.org/10.1016/S0198-8859(02)00753-X
8. Treilleux I, Blay JY, Bendriss-Vermare N, Ray-Coquard I, Bachelot T, Guastalla JP, Bremond A, Goddard S, Pin JJ, Barthelemy-Dubois C, et al. Dendritic cell infiltration and prognosis of early stage breast cancer. Clin Cancer Res 2004; 10:7466-74; PMID:15569976; http://dx.doi.org/10.1158/1078-0432.CCR-04-0684
9. Pascale F, Contreras V, Bonneau M, Courbet A, Chilmonczyk S, Bevilacqua C, Epardaud M, Niborski V, Riffault S, Balazuc AM, et al. Plasmacytoid dendritic cells migrate in afferent skin lymph. J Immunol 2008; 180:5963-72; PMID:18424716
10. Morandi B, Bonaccorsi I, Mesiti M, Conte R, Carrega P, Costa G, Iemmo R, Martini S, Ferrone S, Cantoni C, et al. Characterization of human afferent lymph dendritic cells from seroma fluids. J Immunol 2013; 191:4858-66; PMID:24078697; http://dx.doi.org/10.4049/jimmunol.1300760