

## Special features of quantification of CD8<sup>+</sup>CD38<sup>+</sup> T-cells by flow cytometry does not represent a good biomarker to monitor the reactivation of cytomegalovirus infection after allogeneic hematopoietic stem cell transplantation

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CD38 also known as cyclic ADP ribose hydrolase is a surface glycoprotein expressed by several leukocytes, in particular CD4<sup>+</sup> and CD8<sup>+</sup> T-cells, B-lymphocytes and natural killer cells.<sup>(1)</sup>

CD38 is part of a large family of nucleotide-metabolizing ectoenzymes that also includes CD26, CD39 and CD73. These molecules are clustered in specialized areas of the cell membrane, playing roles as receptor signaling molecules thus regulating cell activation, defense from pathogens, cell migration, immune synapse formation and also life cycle.<sup>(2)</sup>

CD38 is a powerful disease biomarker for several human disorders, including leukemias and myelomas, and also directly involved in the pathogenesis and prognosis of human virus infections. Several potential clinical applications of CD38 as a putative laboratorial biomarker in the diagnosis, prognosis and therapy of viral infections have been previously reported.<sup>(2)</sup>

Elevated CD38 antigen expression on CD8<sup>+</sup> T cells has been pointed out as a stronger marker for the risk of chronic HIV disease progression to AIDS.<sup>(3)</sup> Moreover, recent studies have demonstrated that a parallel decline of CD8<sup>+</sup>CD38<sup>+</sup> lymphocytes and viremia may occur in treated hepatitis B patients, suggesting its role as a biomarker for active infection.<sup>(4)</sup>

It has been proposed that monitoring of the CD8<sup>+</sup>CD38<sup>+</sup> T-cell subset in peripheral blood represents a powerful approach to detect cytomegalovirus (CMV) infections in kidney transplant recipients.<sup>(5)</sup> More recently, it has been reported that in fact, the monitoring of CD38 high expression in peripheral blood CD8<sup>+</sup> lymphocytes is a useful additional diagnostic marker for CMV infection in patients after kidney transplantation, especially when they are at risk of tissue-invasive disease when CMV DNA copies may not be detectable in peripheral blood.<sup>(6)</sup>

The questions surrounding CD38 are still fascinating and continue to prompt novel investigations. One important matter to be clarified is whether the overexpression of the CD38 molecule by circulating T cells may represent a universal biomarker for CMV infection after all modalities of organ transplantation. In order to address this issue, Lino et al.<sup>(7)</sup> performed a prospective investigation to clarify the applicability of flow cytometric enumeration of CD8<sup>+</sup>CD38<sup>+</sup> T-cells in peripheral blood as a laboratorial indicator of CVM infection/reactivation in allogeneic hematopoietic stem cell (HSCT) recipients.

The data presented in this study revealed that, in contrast to those previously published in kidney transplantation, the overexpression of CD38 in circulating CD8<sup>+</sup> T cells does not correlate with the presence on CMV antigenemia. The authors present a plausible explanation for this phenomenon, discussing the particularities of CD38 expression during bone marrow repopulation and immune system reconstitution after HSCT. The cyclic nature of CD38 expression during hematopoietic ontogeny may explain the presence of CD38 overexpression even in those HSCT recipients with undetectable antigenemia. It has been reported that CD38 is expressed early in hematopoietic cells, with downregulation during the cell maturation process and re-expression upon cell activation. This knowledge is relevant to aware flow cytometry readers and medical professionals working in the clinical management of transplant recipients that overexpression of CD38 may not be considered a universal biomarker of CMV infection following organ transplantation.

The article is well organized, presenting the technical details necessary to ensure its reproducibility, excellent scientific quality and promises a fruitful reading.

### References

1. Orciani M, Trubiani O, Guarnieri S, Ferrero E, Di Primio R. CD38 is constitutively expressed in the nucleus of human hematopoietic cells. *J Cell Biochem.* 2008;105(3):905-12.
2. Malavasi F, Deaglio S, Funaro A, Ferrero E, Horenstein AL, Ortolan E, et al. "Evolution and function of the ADP ribosyl cyclase/CD38 gene family in physiology and pathology". *Physiol Rev.* 2008; 88(3):841-86.

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3. Liu Z, Cumberland WG, Hultin LE, Prince HE, Detels R, Giorgi JV. Elevated CD38 antigen expression on CD8<sup>+</sup> T cells is a stronger marker for the risk of chronic HIV disease progression to AIDS and death in the Multicenter AIDS Cohort Study than CD4<sup>+</sup> cell count, soluble immune activation markers, or combinations of HLA-DR and CD38 expression. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;16(2):83-92.
4. Cao W, Qiu ZF, Li TS. Parallel decline of CD8<sup>+</sup>CD38<sup>+</sup> lymphocytes and viremia in treated hepatitis B patients. *World J Gastroenterol.* 2011;17(17):2191-8.
5. Belles-Isles M, Houde I, Lachance JG, Noël R, Kingma I, Roy R. Monitoring of cytomegalovirus infections by the CD8<sup>+</sup>CD38<sup>+</sup> T-cell subset in kidney transplant recipients. *Transplantation.* 1998;65(2):279-82.
6. Ticha O, Stouracova M, Kuman M, Studenik P, Freiburger T, Litzman J. Monitoring of CD38<sup>high</sup> expression in peripheral blood CD8<sup>+</sup> lymphocytes in patients after kidney transplantation as a marker of cytomegalovirus infection. *Transpl Immunol.* 2010;24(1):50-6.
7. Lino VA, Santos SM, Bittencourt HN, Silva ML, Spizziri T, Bretas R, et al. Usefulness of the quantification of CD8<sup>+</sup>CD38<sup>+</sup> lymphocytes by flow cytometry to monitor infection/reactivation of cytomegalovirus after allogeneic hematopoietic stem cell transplantation. *Rev Bras Hematol Hemoter.* 2011;33(4):268-73.