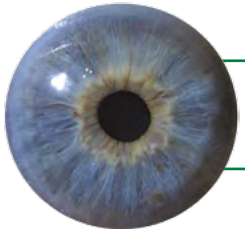

Visión del autor

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Natural killer (NK) cell-derived extracellular-vesicle shuttled microRNAs control T cell responses

Sara G. Dosil[1,2,3]; Sheila López-Cobo[5,#]; Ana Rodríguez-Galán[1,2,3]; Irene Fernández-Delgado[1,2,3]; Paula Milán-Rois[4]; Milagros Castellanos[4]; Álvaro Somoza[4]; Manuel José Gómez[2]; Hugh T. Reyburn[5]; Mar Valés-Gómez[5]; Francisco Sánchez-Madrid[1,2,3,*]; Lola Fernández-Messina[1,2,3,6]

[1]Immunology Service, Hospital de la Princesa, Universidad Autónoma de Madrid, Instituto Investigación Sanitaria Princesa, Madrid, Spain; [2]Intercellular Communication in the Inflammatory Response. Vascular Pathophysiology Area, National Center for Cardiovascular Research (CNIC), Madrid, Spain;[3]Universidad Autónoma de Madrid, Madrid, Spain; [4]Instituto Madrileño de Estudios Avanzados en Nanociencia (IMDEA Nanociencia) & Nanobiotecnología (IMDEA-Nanociencia), Unidad Asociada al Centro Nacional de Biotecnología (CSIC), Madrid, Spain; [5]Department of Immunology and Oncology, National Centre for Biotechnology, Spanish National Research Council, Madrid, Spain; [6]CIBER de Enfermedades Cardiovasculares (CIBERCV), Madrid, Spain; [#]Current address: INSERM U932, Institut Curie, PSL Research University, Paris, France.

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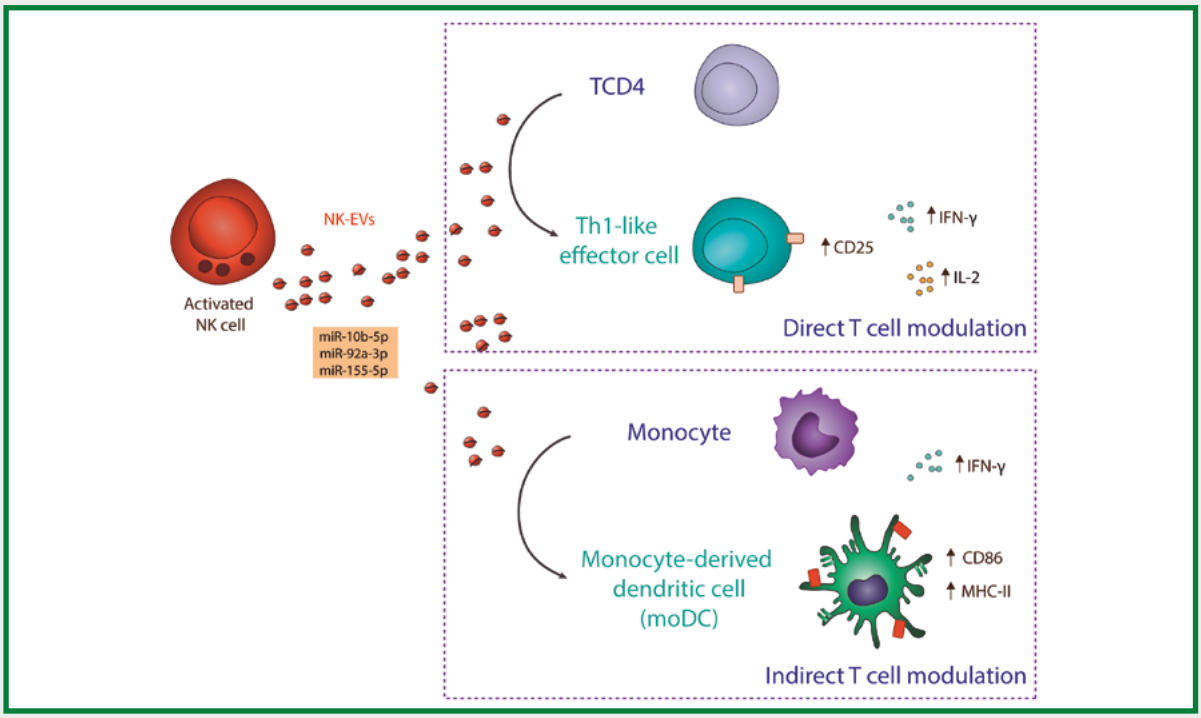
Natural killer (NK) cells play a key role as innate immune effectors, capable of recognising and killing cells undergoing different types of stress and of regulating immune responses, in particular T cell function. Interestingly, NK lymphocytes are capable of releasing extracellular vesicles, including exosomes, that bear lytic molecules, such as Fas-ligand or perforin. Recent evidence supports that these vesicles can exert antitumoural functions in pre-clinical models. However, the immunomodulatory effects of NK-derived extracellular vesicles (NK-EVs) are far from being fully elucidated.

In this work, small RNA next-generation sequencing from resting NK cells, activated NK cells and their released EVs identified a specific signature of NK-EV microRNAs that bear a specific pattern of non-templated nucleotide additions and are enriched with short-sequence motifs. MicroRNAs preferentially sorted into NK-EVs, namely miR-10b-5p, miR-92a-3p and miR-155-5p, were found to target mRNA molecules involved in Th1-related functions. Moreover, NK-EV enriched microRNAs were found to promote Th1-skewed immune responses. Directly, by inducing $CD4^+$ T cell polarization via GATA-3 down-modulation and subsequent T-bet de-repression, and driving IFN-γ and IL-2 production; and indirectly, by enhancing monocyte-derived dendritic cells co-stimulatory and presenting functions. Since many tumours and pathogens dampen T helper effector cell-mediated immunosurveillance, many immunotherapeutic approaches have focused in restoring Th1 responses. Thus, we propose that NK-EV mediated immune deviation towards Th1 may be exploited and taken into account when designing EV-based therapies. We also show that targeted delivery of NK-EV enriched microRNAs using microRNA-loaded gold nanoparticles recapitulated the effects of NK-EVs, promoting T cell activation and Th1 like responses.



Altogether, our results provide new insights on the immunomodulatory roles of NK-derived EVs that may pave the way to design new therapeutic strategies, based on NK-EVs and/or targeted delivery of immunotherapeutic microRNAs.

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Por Lola Fernández, Francisco Sánchez y Sara G. Dosil