The commensal Prevotella heparinolytica skews dendritic cells towards a pro-Th17 phenotype and accelerates multiple myeloma progression

Arianna Brevi[1,2]*, Roberto Ferrarese[3], Matteo Grioni[1], Desiree Masciovecchio[1,2], Virginia Amato[1], Laura Cogrossi[1,2], Nicasio Mancini[2,3], Matteo Bellone[1]
*brevi.arianna@hsr.it
[1] Cellular immunology Unit, San Raffaele Scientific Institute, Division of Immunology, Transplantation and Infectious Diseases, Milan, Italy
[2]Vita-Salute San Raffaele University, Milan, Italy
[3]Laboratory of Microbiology, San Raffaele Scientific Institute, Milan, Italy

Keywords (maximum 8): Prevoltella, Dendritic cell, Th17, Multiple myeloma.

Background The host microbiota impact immune responses beyond skin and mucosae. Here we investigated if the gut microbiota favors the induction of pro-tumoral Th17 responses in multiple myeloma, a treatable but incurable neoplasia of plasma cells mainly accumulating in the bone marrow.

Methods For gut colonization with selected commensal bacteria, mice were depleted of their microbiota by antibiotic treatment, and infected with *Prevotella heparinolytica* or *P. melaninogenica* by oral gavage. Immune infiltrates were analyzed by flow cytometry. Dendritic cells (DCs) were differentiated *in vitro* from bone marrow (BM) precursors or $CD14^+$ peripheral blood mononuclear cells and stimulated with heat-killed bacteria. Splenocytes from C57BL/6 mice were stimulated with αCD3/αCD28 beads in the presence of Th17 polarizing cytokines or heat-killed bacteria.

Results Here we show that administration of *P. heparinolytica* but not *P. melaninogenica* to mice affected by multiple myeloma promoted the differentiation of Th17 cells colonizing the Peyer's patches and migrating to the bone marrow, where they favored multiple myeloma aggressiveness. Disturbance of their microbiome or treatment with IL-17 blocking antibodies led to delayed disease appearance. Mechanistically, both heat-inactivated *P. heparinolytica* and *P. melaninogenica* induced murine and human DCs to maturation, but only *P. heparinolytica* prompted DCs to produce IL-1β, thus favoring Th17 differentiation.

Conclusions In mice affected by multiple myeloma, commensal bacteria, and *P. heparinolytica* in particular, unleash a signaling network between adaptive and innate immunity that accelerates MM, and can be targeted by already available therapies.