BIOGRAPHICAL SKETCH

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NAME: Rodriguez, Gloria Marcela

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POSITION TITLE: Associate Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE (if applicable)	END DATE MM/YYYY	FIELD OF STUDY
Pontificia Universidad Javeriana, Bogota	BS	06/1986	Bacteriology
New York University, New York, NY	PHD	05/1999	Microbiology
The Public Health Research Institute, New York, NY	Postdoctoral Fellow	2003	Mycobacteriology

A. Personal Statement

The main focus of the studies in my laboratory is the role of metal homeostasis in host-pathogen interactions. I am particularly interested in the effects of metal ion restriction, resulting from nutritional immunity, on the pathogenesis of M. tuberculosis (Mtb). My early training in biochemistry, cell biology, and immunology, combined with many years in the TB field have given me the right foundation to study the biology of the tuberculous bacillus, and the complex interplay between Mtb and its host.

Overall, the research program in my laboratory combines in vitro, ex vivo, and in vivo approaches to address the molecular mechanisms governing the response of Mtb to metal homeostasis challenges in the host. My group has significantly contributed to the current understanding of the mechanisms of metal acquisition and regulation in mycobacteria. I identified the main iron transporter and virulence determinant IrtAB, defined the iron limitation response of Mtb, and characterized the master regulator of iron metabolism, IdeR. My group deciphered the mechanisms of IdeR dual function as a repressor of iron uptake and activator of iron storage that are essential for Mtb virulence. We defined the role of the iron storage protein ferritin, in antibiotic tolerance and demonstrated its promise as a protective antigen in vaccine studies. We are now conducting translational research to perturb iron homeostasis in Mtb and thereby enhance Mtb susceptibility to endogenous reactive oxygen species and broad spectrum antibiotics. My laboratory also discovered the main manganese (Mn) transporter MntABC and the Mn uptake regulator MntR and contributed to characterize the zinc regulator Zur and their role in Mtb adaptation to the host environment.

In a large collaborative effort, we uncovered the ultimate response of Mtb to Fe-deprivation encountered in the host. It includes survival without replication, upregulation of host survival factors, and enhanced antibiotic tolerance. By highlighting the potential role of nutritional immunity in promoting latent TB infection, this work had clinical implications for the treatment of TB and anemia of iron deficiency, which is the most common nutritional disorder in the world.

We discovered that in response to iron (Fe) limitation, Mtb increases the production of extracellular vesicles with strong potential for immunomodulation and pathogenesis. Most recently, we uncovered the requirement of the mycobacterial dynamin-like proteins for vesicle biogenesis in Mtb. Our current research combines multiple approaches to understand the mechanisms driving vesicle production and their role during infection.

1. Gupta S, Palacios A, Khataokar A, Weinrick B, Lavin JL, Sampedro L, Gil D, Anguita J, Menendez M, Garcia M, Dogra N, Neiditch MB, Prados-Rosales R, Rodriguez G. Dynamin-like proteins are essential for Vesicle biogenesis in Mycobacterium tuberculosis. BioRxiv. 2020 January 15. DOI:

https://doi.org/10.1101/2020.01.14.906362

2. Gupta S, Rodriguez GM. Mycobacterial extracellular vesicles and host pathogen interactions. Pathog Dis. 2018 Jun 1;76(4) PubMed Central PMCID: PMC5930244.
3. Marcela Rodriguez G, Neyrolles O. Metallobiology of Tuberculosis. Microbiol Spectr. 2014 Jun;2(3) PubMed Central PMCID: PMC5180607.
4. Prados-Rosales R, Weinrick BC, Piqué DG, Jacobs WR Jr, Casadevall A, Rodriguez GM. Role for Mycobacterium tuberculosis membrane vesicles in iron acquisition. J Bacteriol. 2014 Mar;196(6):1250-6. PubMed Central PMCID: PMC3957709.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2019 -	Associate Professor, Rutgers University, Rutgers University, Livingston, NJ
2007 - 2018	Assistant Professor, Public Health Research Institute, . New Jersey Medical School-Rutgers the State University of New Jersey, Newark, NJ
2003 - 2006	Research Associate Member, Public Health Research Institute, University of Medicine and Dentistry of New Jersey, Newark, NJ
1999 - 2003	Post-doctoral Fellow, Public Health Research Institute, New York, NY
1995 - 1999	Graduate Student, New York University, New York, NY
1990 - 1994	Research Assistant, New York Unversity, New York, NY
1986 - 1990	Research Assistant, Instituto de Immunologia, Bogota

Honors

2011	Faculty award, Hispanic Center for Excellence. University of Medicine and Dentistry of New Jersey.
2001	Fellowship in Pulmonary Research, Parker B. Francis Foundation
1999	Postdoctoral Fellowship, UNCF-Parke Davis

C. Contribution to Science

1. My first publications were in the field of immunology and cell biology of antigen processing and presentation in the context of MHC class II molecules. In those studies, I characterized the activity of the cathepsins D and B in antigen processing and the nature of the cellular compartments where they function. Importantly, the result of that work was one of the first demonstrations that in contrast to MHC class I molecules, MHC class II molecules could bind and present long peptides. This discovery had broad implications for epitope analysis and design.

    a. Rodriguez GM, Diment S. Destructive proteolysis by cysteine proteases in antigen presentation of ovalbumin. Eur J Immunol. 1995 Jul;25(7):1823-7. PubMed PMID: 7621859.
    b. Diment S, Eidelman M, Rodriguez GM, Orlow SJ. Lysosomal hydrolases are present in melanosomes and are elevated in melanizing cells. J Biol Chem. 1995 Mar 3;270(9):4213-5. PubMed PMID: 7876179.
    c. Rodriguez GM, Diment S. Role of cathepsin D in antigen presentation of ovalbumin. J Immunol. 1992 Nov 1;149(9):2894-8. PubMed PMID: 1328388.

2. In the field of tuberculosis pathogenesis, my main contributions have been in the area of iron acquisition and regulation. Iron plays an essential role in host-pathogen interactions because it is essential, elusive, and potentially toxic. To proliferate, pathogens must compete for iron in the host and tightly regulate intracellular iron levels to avoid toxic effects of excess iron. I reported for the first time the gene expression response of M. tuberculosis to changes in iron availability and identified IdeR as the central regulator of iron uptake and storage. I also demonstrated the essentiality of IdeR

for M. tuberculosis survival in the host. Furthermore, I discovered IrtAB, the main iron transporter in M. tuberculosis and demonstrated its role in virulence. We also reported on the role of iron storage proteins in virulence, protection against iron deficiency, oxidative stress, and antibiotics. We demonstrated that immunization with a ferritin (bfrB) mutant could confer protection against subsequent infection with virulent M. tuberculosis in a mouse model. My group contributed to define the role of the type VII secretion system ESX-3 in iron acquisition in Mtb. Lastly, my group provided evidence of iron starvation-induced nonreplicative persistence of Mtb in vitro that correlated with host imposed iron deprivation in certain microenvironments of human granulomas. This is clinically relevant and can help explain the long-known risk of TB reactivation upon iron supplementation to treat anemia.

a. Kurthkoti K, Amin H, Marakalala MJ, Ghanny S, Subbian S, Sakatos A, Livny J, Fortune SM, Berney M, Rodriguez GM. The Capacity of *Mycobacterium tuberculosis* To Survive Iron Starvation Might Enable It To Persist in Iron-Deprived Microenvironments of Human Granulomas. mBio. 2017 Aug 15;8(4) PubMed Central PMCID: PMC5559634.
b. Pandey R, Rodriguez GM. IdeR is required for iron homeostasis and virulence in Mycobacterium tuberculosis. Mol Microbiol. 2014 Jan;91(1):98-109. PubMed Central PMCID: PMC3902104.
c. Pandey R, Rodriguez GM. A ferritin mutant of Mycobacterium tuberculosis is highly susceptible to killing by antibiotics and is unable to establish a chronic infection in mice. Infect Immun. 2012 Oct;80(10):3650-9. PubMed Central PMCID: PMC3457556.
d. Ryndak MB, Wang S, Smith I, Rodriguez GM. The Mycobacterium tuberculosis high-affinity iron importer, IrtA, contains an FAD-binding domain. J Bacteriol. 2010 Feb;192(3):861-9. PubMed Central PMCID: PMC2812465.

3. Manganese and Zinc transport and regulation in M. tuberculosis: Although Fe-restriction is the most prominent and well-understood example of nutritional immunity, Mn and Zn sequestration has recently emerged as an important mechanism of host resistance to several bacterial and fungal infections. Our studies discovered key Mn homeostatic mechanisms in Mtb comprising an Mn dependent transcriptional regulator and two Mn transporters, MntH and MntABCD. We found that Mtb strains deficient for Mn import are highly sensitive to conditions of low Mn availability and fail to proliferate macrophages. We also contributed to the identification and characterization of Zur, a transcriptional regulator that controls the Mtb response to Zn limitation.

   a. Pandey R, Russo R, Ghanny S, Huang X, Helmann J, Rodriguez GM. MntR(Rv2788): a transcriptional regulator that controls manganese homeostasis in Mycobacterium tuberculosis. Mol Microbiol. 2015 Dec;98(6):1168-83. PubMed Central PMCID: PMC5157835.
   b. Serafini A, Pisu D, Palù G, Rodriguez GM, Manganelli R. The ESX-3 secretion system is necessary for iron and zinc homeostasis in Mycobacterium tuberculosis. PLoS One. 2013;8(10):e78351. PubMed Central PMCID: PMC3796483.
   c. Maciag A, Dainese E, Rodriguez GM, Milano A, Provvedi R, Pasca MR, Smith I, Palù G, Riccardi G, Manganelli R. Global analysis of the Mycobacterium tuberculosis Zur (FurB) regulon. J Bacteriol. 2007 Feb;189(3):730-40. PubMed Central PMCID: PMC1797298.

4. Iron dependent regulation of vesiculation in Mtb. We discovered that increased production of membrane vesicles is part of the response of Mtb to iron-limited conditions as encountered in the host. In addition, we uncovered distinct composition of vesicles produced under iron limitation including the presence of a potent siderophore that can function in adaptation to iron limitation. This opens a new chapter in the study of mechanisms used by Mtb to interact with the host. Our most recent studies on the mechanisms of iron-regulated membrane vesicle production uncovered an essential role for the dynamin-like proteins IniA and IniC in the release of membrane vesicles by Mtb in culture and during macrophage infection. This work has open the way to understanding the mechanistic aspects of vesicle production and their role in vivo during infection.

a. Gupta S, Palacios A, Khataokar A, Weinrick B, Lavin JL, Sampedro L, Gil D, Anguita J, Menendez M, Garcia M, Dogra N, Neiditch MB, Prados-Rosales R, Rodriguez G. Dynamin-like proteins are essential for Vesicle biogenesis in Mycobacterium tuberculosis. BioRxiv. 2020 January 15. DOI: https://doi.org/10.1101/2020.01.14.906362
b. Gupta S, Rodriguez G. Isolation and Characterization of Extracellular Vesicles produced by iron-limited Mycobacteria. Journal of visualized experiments : JoVE. 2019 October 31; 152. Available from: e60359 DOI: doi:10.3791/60359
c. Rodriguez GM, Prados-Rosales R. Functions and importance of mycobacterial extracellular vesicles. Appl Microbiol Biotechnol. 2016 May;100(9):3887-92. PubMed Central PMCID: PMC4879809.
d. Prados-Rosales R, Weinrick BC, Piqué DG, Jacobs WR Jr, Casadevall A, Rodriguez GM. Role for Mycobacterium tuberculosis membrane vesicles in iron acquisition. J Bacteriol. 2014 Mar;196(6):1250-6. PubMed Central PMCID: PMC3957709.

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