FSMAC Funded Canadian Researcher

Dr. Rashmi Kothary
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Biosketch:

Dr. Kothary is the Deputy Scientific Director and Senior Scientist at the Ottawa Hospital Research Institute (OHRI). He received a Ph.D. in Biochemistry from the University of British Columbia and pursued postdoctoral research in the laboratories of Dr. Janet Rossant at the Mount Sinai Hospital Research Institute in Toronto and Dr. Azim Surani in Cambridge. It was during these formative years that Dr. Kothary developed his interest in the use of preclinical animal models to study disease pathology. In 1998, Dr. Kothary moved to Ottawa where he has been ever since. He held the University Health Research Chair in Neuromuscular Disorders and is a Professor at the University of Ottawa. His research focuses on investigating factors important for oligodendrocyte mediated myelination and remyelination of the central nervous system, and understanding Spinal Muscular Atrophy pathogenesis and identifying novel therapeutics for this devastating children's disease. He has served on the scientific advisory board for MDA and Cure SMA, and is a reviewer for the NIH. A highlight for him is his participation in the annual Cure SMA Conference where researchers and families meet. He has attended this meeting since 2000 and is inspired by the positive spirit of the kids and their families.

Highlights from three recent publications in late 2016 from Dr. Kothary's team:

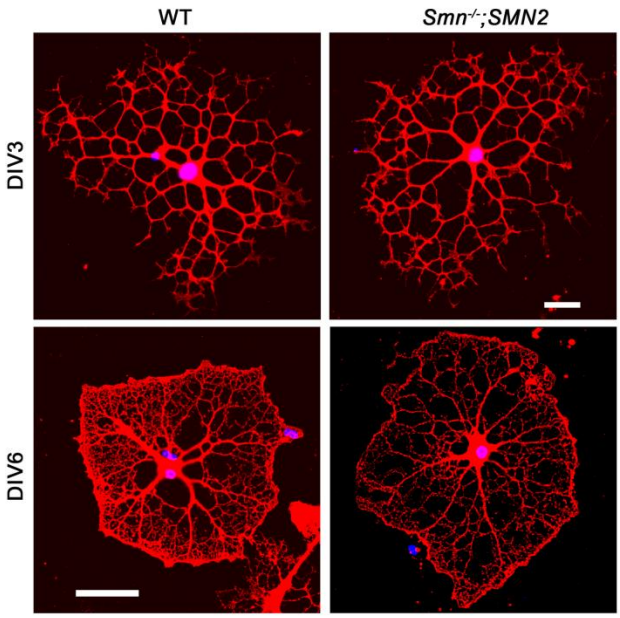
1. Research helps unravel complex genetics of Spinal Muscular Atrophy
Authors: Mehdi Eshraghi, Emily McFall, Sabrina Gibeault, Rashmi Kothary

Spinal Muscular Atrophy (SMA) is a neuromuscular disease caused by mutations or deletions in the Survival Motor Neuron1 (*SMN1*) gene. However, some people with the exact same mutations suffer much more severe symptoms than others. We have recently published a paper in *Human Molecular Genetics* that supports the theory that other genes also play an important role in this disease. We compared SMA animal models from two different genetic backgrounds, and found animals from one background lived longer (on average 25 days instead of 19), lost weight at a slower rate, and developed muscle weakness and nerve loss in the spinal cord at a later age. The difference seems to be linked to a gene called Plastin 3, but other genes are likely at play as well. Identifying these could provide new targets for drug development.

2. Myelin producing cells of the CNS are not affected in Spinal Muscular Atrophy

Authors: Ryan O'Meara, Sarah Cummings, Yves De Repentigny, Emily McFall, John-Paul Michalski, Marc-Olivier Deguise, Sabrina Gibeault, Rashmi Kothary

Spinal muscular atrophy (SMA) is classically considered a disease of the motor neuron resulting from insufficient levels of the survival motor neuron (SMN) protein. Increasing evidence now supports SMA as a multi-system disorder, affecting many other cell types in the nervous system, as well as the pancreas, spleen and thymus, just to name a few. In work published by our team in *Human Molecular Genetics*, we investigated the impact of SMN depletion on another cell type in the nervous system: the oligodendrocyte. The oligodendrocyte produces myelin in the central nervous system and plays important roles in promoting signal transduction, providing support to the axons and protecting axons from damage. An extensive assessment was performed, taking advantage of a severe mouse model of SMA. In all experiments conducted on this cell type, there were no differences detected in oligodendrocytes derived from a mouse with depleted SMN levels (see image). These results were surprising. Although several organs and cell types are affected, we know that some are more affected than others. Exploring this unaffected cell type (oligodendrocytes) further, may help us to identify a mechanism in these cells that is protective against the loss of SMN. Any such mechanism could then be applied to the cell types dramatically affected in SMA in the hopes of identifying a means to promote their development and function.



3. Immune system dysfunction in Spinal Muscular Atrophy

Authors: Marc-Olivier Deguise, Yves De Repentigny, Emily McFall, Nicole Auclair, Subash Sad, Rashmi Kothary

Spinal muscular atrophy (SMA) has long been considered as a disease of the motor neuron. However, recent work has highlighted defects in many other cell types that could be contributing to the development of SMA. In this context, the immune system has never been extensively studied. Defects in immune function could exacerbate disease progression by causing inflammation in the spinal cord or making patients more susceptible to bacterial or viral infections. Now, in work published by our team in *Human Molecular Genetics*, we show severe alterations in two organs of the immune system, namely the thymus and spleen, in two different mouse models of SMA. More specifically, the spleen was dramatically smaller at a

very young age (see image which shows the spleen from normal mice and from a SMA mouse model named *Smn*$^{2B/-}$) and the immune cells it contains were not in their usual location within the organ. As well, the internal structure of the thymus showed many abnormalities. The thymus is important in maturation of one type of immune cell called the T-cell. Therefore, we investigated if T-cell maturation was the cause of the abnormalities in the spleen and thymus. Indeed, we found that T-cell maturation was impaired but not causative of the spleen defects. The spleen has multiple functions including blood filtration for old blood cells, microbes and keeping normal levels of iron. Therefore, our findings highlight the possibility that any of these functions might be impaired. More importantly, abnormal T-cell development and deficient filtration of microbes from the spleen highlights the possibility that SMA patients may be more likely to be sick from infection caused by bacteria or virus.