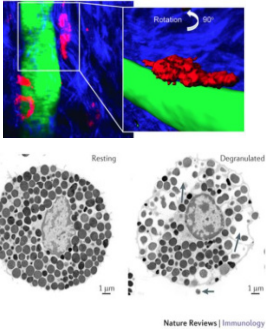


INTRODUCTION

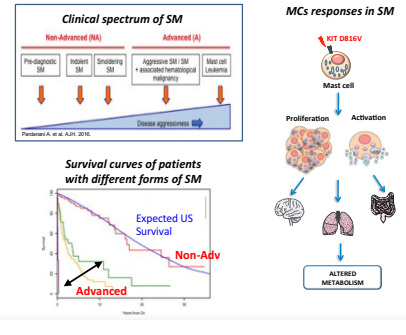
MAST CELLS ARE SENTINELS OF THE IMMUNE SYSTEM



Cellular metabolism controls cell function, yet little is known about the metabolic reprogramming in mast cells (MC). MC are sentinels of the immune system that reside close to blood vessels and nerves in tissues that serve as a barrier to the external environment. MC activation is involved in the response to a variety of pathogens and allergens, making these cells an important effector type in innate immunity but also in allergic reactions and asthma.

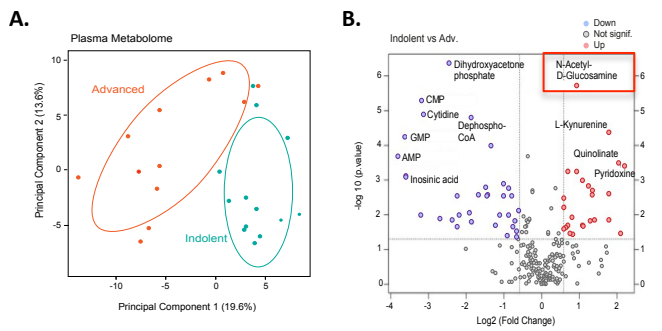
Alterations in the number and reactivity of MCs are typical features of systemic mastocytosis (SM), a myeloproliferative disorder characterized by an increase in MCs burden in organs leading to systemic metabolic alterations. SM ranges from indolent to severe, leukemic rapidly fatal forms with limited therapeutic options; all forms harboring the same D816V mutation in the receptor tyrosine kinase KIT. The aim of this study is to determine if potential oncometabolites are responsible for SM severity and regulate MCs effectors functions.

SYSTEMIC MASTOCYTOSIS CLASSIFICATION

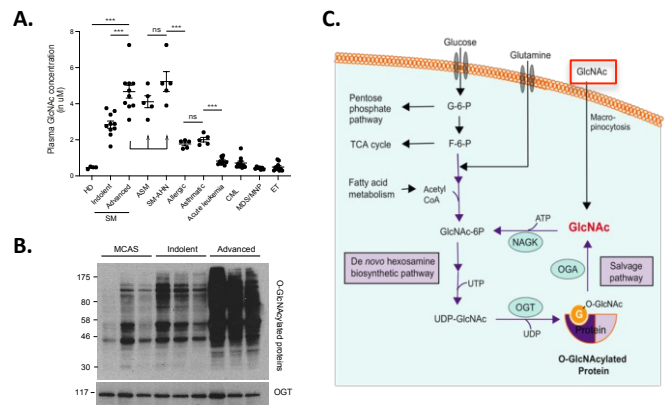


RESULTS

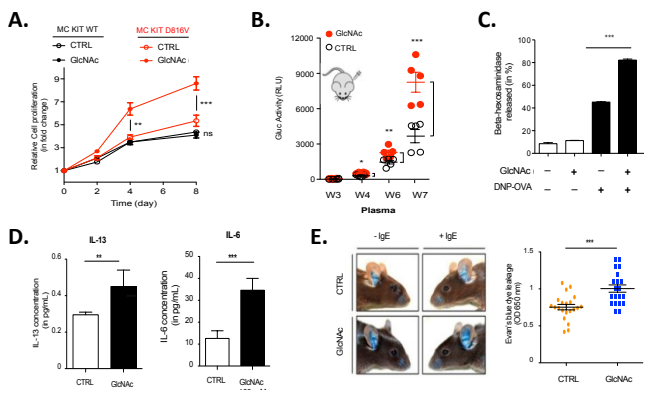
1/ METABOLIC ALTERATIONS ASSOCIATED WITH SM SEVERITY



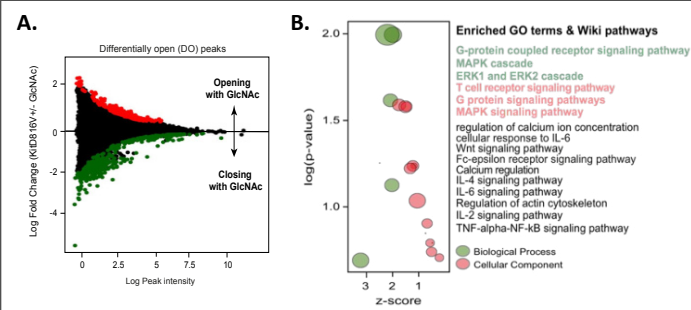
2/ GlcNAc IS A CIRCULATING BIOMARKER OF SM SEVERITY



3/ GlcNAc INCREASES MCs PROLIFERATION AND ACTIVATION



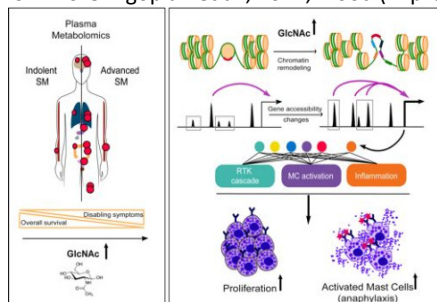
4/ GlcNAc MODULATES KIT D816V MCs CHROMATIN ACCESSIBILITY



CONCLUSION

- ✓ Plasma metabolomic profiles discriminate indolent from advanced SM.
- ✓ GlcNAc is an oncometabolite driver of SM. (Patent B3494EP00)
- ✓ In presence of exogenous GlcNAc, MCs showed abnormal proliferation and responded with exaggerated responses to normal stimuli, leading to unrestrained inflammation.
- ✓ GlcNAc modulates neoplastic MCs chromatin accessibility to transcription of regions containing genes coding for effectors of Receptor Tyrosine Kinase signaling (MAPK, ERK cascade), MCs activation (FceRI, Fyn) and inflammation (cytokines).

To know more: Agopian et al., 2021, Blood (in press)



Our results suggest that the manipulation of metabolic pathways critically influences mast cells effectors functions, and could be used for developing novel strategies to modulate mast cell responses.

ACKNOWLEDGMENTS



* **Contact:**
fabienne.brenet@inserm.fr