**Poster 14: New insights in mastocytosis physiopathology provided by genetic study of familial forms**

Marc Rassy 1.2.3 *, Kitsada Kangboonruang 1 , Patrice Dubreuil 4, Laurent Gros 5, Julien Rossignol 1, Laura Polivka 1, Genevieve De Saint Basile 1, Christine Bodemer 6, Olivier Hermine 1, Leila Maouche Chretien 1
1 : Imagine - Institut des maladies genetiques (IHU), Institut National de la Sante et de la Recherche Medicate : U1163, Universite Paris Cite: UMR_S 1163
2 : ANRT, Cifre
3 : AB Science, AB Science Institut Paoli-Calmettes - Service Biopathologie
4 : Centre de Recherche en Cancerologie de Marseille, Centre National de la Recherche Scientiflque - CNRS : UMR7258, Institut National de la Sante et de la Recherche Medicate - INSERM: U1068, Institute of Paoli-Calmettes(IPC): UMR7258, A ix-Marseille Universite -AMU: UM/05
5 : AB Science, AB Science Institut Paoli-Calmettes - Service Biopathologie
6: Service de dermatologie [CHU Necker], assistance publique - Hôpitaux de Paris (AP-HP), CHU Necker - Enfants Malades [AP-HP]
*: Auteur correspondant

Mastocytosis is a rare heterogenous disease despite the frequent somatic KIT D8 l 6V mutation. We hereby study familial mastocytosis to find concurrent mutations potentially involved in its physiopathology.
In this retrospective study, we have performed whole exome sequencing on DNA from peripheral blood mononuclear cells of a total of 17 individuals from 3 distinct families (6 patients diagnosed with mastocytosis, 6 healthy related individuals, and 5 with allergy symptoms).
Using our own bioinformatic pipeline on all 64108 annotated variants, we have identified 226 variants affecting 81 genes in mastocytosis patients of at least 2 families. Among the candidates, the LMTK3 gene stood out because of its mutational profile in mastocytosis patients, its expression in mast cells from public and private databases, and its properties from the literature.
In our cohort, the LMTK3 gene had an exon 12 missense mutation in 2 related mastocytosis patients. Similarly, a missense mutation and an insertion with frameshift was found in exon 12 of a mastocytosis patient of another family. No LMTK3 protein-impacting variant was found in the remaining, healthy or allergic, members of the 2 families.
According to the F ANTOM dataset, cutaneous mast cells from healthy individuals show no LMTK3 RNA expression, even after culture and/or stimulation. Interestingly, moderate RNA expression of LMTK3 is found in bone marrow mast cells from sporadic systemic mastocytosis patients. LMTK3 RNA expression is also found in HMC 1.2, a conventional mastocytosis cell line harboring the KIT D816V mutation. The impact of our mutations on LMTK3 expression remains unknown.
According to the literature, LMTK3 is a serine threonine kinase overexpressed in solid tumors ( e.g. breast cancer) and hematopoietic cancers ( chronic neutrophilic leukemia). It can be targeted by selective potent inhibitors. The interaction between LMTK3 and KIT has been investigated in gastrointestinal tumors and melanomas. LMTK3 is a KIT-specific translation regulator. LMTK3 inhibition kills KIT-dependent cells and slows tumor progression in viva. To our knowledge, no significant studies have investigated LMTK3 in mast cell neoplasms.
Our approach suggests a role of LMTK3 in familial and sporadic mastocytosis. Further studies are needed to decipher the mechanistic link between LMTK3 and traditional KIT D8 l 6V mutations in mastocytosis. Combining KIT and LMTK3 inhibitors may represent a new therapeutic option of mastocytosis.