POSTER 8: Familial genetic study reveals potential AXL involvement in mastocytosis physiopathology and treatment

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Mastocytosis is a rare hematological disease characterized by an abnormal accumulation of mast cells in the skin or in several organs. 85% of patients carry the somatic D8 l 6V mutation in the KIT gene. However, tyrosine kinase inhibitors (iTKs) have been shown to be ineffective in many cases, suggesting the involvement of other genes in mastocytosis. Other evidence is patients carrying KIT D816V mutation present varied symptoms and very heterogeneous degrees of disease severity. Moreover, several cases of familial forms of mastocytosis have been reported indÎcating the involvement of inherited genetic factors.

The objective of our study was to identify new causative pathways of mastocytosis, in addition to KIT pathway, by searching for mutated genes in familial forms. We selected five familial cases of mastocytosis and perform a family-based exome sequencing approach. We identified AXL, a gene involved in various cancers and resistance to TK!s. We detected two very rare mutations in AXL gene of 4 patients from two unrelated families, which are a missense mutation in exon 12 of AXL (AXL G334S) and a missense mutation in exon 5 (AXL L197M). AXL G334S mutation is found in three young sisters harboring different mutations on the KITgene. AXL L197Mmutation is found in one patient carrying KIT D816Vmutation. To assess the role of AXL and its signaling pathway in the onset of mastocytosis, different human mast cell models were transduced with lentiviral vectors expressing AXL WT, AXL L197M or AXLG334S.

Our result showed that AXL WT or AXL Ll97M alone has no effect on cell proliferation in ROSA KIT WT cells, whereas in the presence of KIT D816V, AXL L197Mslightly enhance cell proliferation in ROSA KIT D816V cells partly through the induction ofp-FAK, p-STAT3, MCL-1 and Bel-XL. In HMCl.2 cells that express both KIT D816V and KIT G560V, AXL WT andAXL mutations enhance cell survival after PKC412 treatment which is FDA-approved iTK. Interestingly, AXL G334S has the highest survival effect. PKC412 decrease the expression level of AXL in HMCl.2 cells whereas it has no effect on AXL expression in HMCl.2 with AXLG334S which may explain the highest survival rate. Moreover, both AXL mutations also enhance cell survival rate in human primary mast cells. This research demonstrated, for the first time, the involvement of AXL in mastocytosis, leading to the identification of promising new therapeutic targets.