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**Title:** Decreased tryptophan and increased kynurenine levels in mastocytosis associated with digestive symptoms

**Short title:** Kynurenine pathway in digestive mastocytosis.

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**Abbreviations:**

ASM: aggressive systemic mastocytosis

AHNMD: associated clonal haematological non-MC-lineage disease.

CM: cutaneous mastocytosis

HPLC: high-performance liquid chromatography

IDO: Indoleamine 2,3-dioxygenase

ISM: indolent systemic mastocytosis

KYN: Kynurenine

MC: Mast Cell

5-HT: Serotonin

TRP: Tryptophan

WT: wild type

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Gene sequencing: ES, KH, PD

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Provision of study materials: S G-L, AS, GD, M-O C, SB, OL, French mast cell study group, OH and HS

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The main metabolism pathway of tryptophan is protein formation, but it can also be metabolized into serotonin and kynurenine. Indoleamine 2,3-dioxygenase (IDO) is the enzyme that catalyzes the degradation of tryptophan into kynurenine. Mastocytosis is a heterogeneous disease characterized by mast cell accumulation in various tissues with 57% of patients having gastrointestinal involvement. We studied tryptophan metabolism in mastocytosis patients displaying or not gastrointestinal features and healthy subjects (n=26 in each group). Mastocytosis patients with digestive symptoms displayed significantly increased kynurenine level and IDO activity as compared to healthy controls and mastocytosis patients without digestive symptoms. This could be linked to mast cell mediated digestive inflammation among patients with mastocytosis. This work is the first focusing on kynurenine pathway in a mast cell disease and could help to understand the pathogenesis of digestive features in mastocytosis as well as in other mast cell mediated diseases.

**Key words:** IDO, kynurenine, mastocytosis, serotonin, tryptophan.

## Introduction

Tryptophan (TRP) is an essential amino acid which is the precursor of serotonin (5-HT) and its availability is the rate-limiting step in the synthesis of 5-HT (1). TRP is mostly involved in protein synthesis but is also the precursor of 5-HT or can be catabolized in the kynurenine (KYN) pathway (1). The main enzyme that catalyzes TRP conversion into KYN is indoleamine 2,3-dioxygenase (IDO, EC 1.13.11.17) (1)1–4). . IDO activity can be induced in various immune cells including mast cells by inflammatory cytokines (2) (figure 1). TRP and its metabolites play a role in intestinal immunity, inflammation and gut motility through 5-HT (4)(4).

Mastocytosis is a heterogeneous disease characterized by mast cell accumulation in various tissues (6). Clinical manifestations of mastocytosis are related to MC mediators release and to pathological MC infiltration (6,7). Mastocytosis patients display disabling gastrointestinal symptoms (59%) including(9,10) diarrhoea, bloating, nausea and abdominal pain (9,10)(9,10). Although, normal human MC are able to synthesize and release 5-HT (11), mastocytosis patients with diarrhea have abnormally low 5-HT (12).

Our aim was to investigate TRP metabolism in mastocytosis by comparing patients displaying gastrointestinal features to healthy controls and mastocytosis patients without gastrointestinal features.



## **Patients and methods**

### *Patients and controls*

Adults with mastocytosis (n=52), as defined by the WHO international consensus criteria (6) were enrolled in a prospective national multicentric French study between 2007 and 2013. Patients with digestive features (n=26), as defined by our previous report were compared to subjects with mastocytosis but without digestive features, matched in sex and age and randomly selected in the French mastocytosis center (n=26) (9). Gastro-intestinal symptoms taken into account were bloating, abdominal pain, nausea ( $\geq 5$  times/week), vomiting ( $\geq 1$  time/week), and liquid stools ( $> 5$  times/week). All patients provided their informed consent. The study was approved by the ethics committee at Necker hospital, and was carried out in compliance with the precepts of the Helsinki protocol. Healthy subjects with neither digestive symptoms nor mastocytosis were used as controls.

*Serum tryptase, plasma tryptophan, whole blood serotonin and plasma kynurenine measurements (figure 2).*

Serum total tryptase was measured using fluorescent enzyme-linked immunoassay (Unicap; Pharmacia) (14). Whole blood serotonin and plasma TRP rates and KYN were determined by high-performance liquid chromatography (HPLC) (16). IDO activity (= KYN/TRP ratio) was calculated from absolute concentrations of KYN and TRP (17).

### *Statistical analysis*

Statistical comparisons were performed using ANOVA and Wilcoxon non parametric tests (GraphPad Prism software version 5.01, GraphPad Software Inc., San Diego, CA) when appropriate. All reported *p* values were two-tailed with a significance level of 0.05

## **Results**

### **Main features of the study population (supplementary tables)**

The characteristics of the patients are described in supplementary Tables. As expected, all mastocytosis patients displayed significantly higher tryptase serum rates than healthy controls ( $p < 0.0001$ ) (fig.2.A) Seven patients had undergone digestive endoscopic explorations with proven mast cell infiltration on histological biopsies (Supplementary figure 1). In mastocytosis patients, digestive features were respectively: diarrhoea (53.9%), abdominal pain (42.3%), bloating (34.6%), nausea (19.2%) and vomiting (11.5%).

### **Patients with digestive features displayed higher IDO activity and higher levels of Kynurenine.**

Compared to healthy controls, mastocytosis patients displayed lower levels of TRP ( $p < 0.0001$ ) independently from GI symptoms. However, only those with gastrointestinal symptoms had higher IDO activity compared to controls (Figure 2.B;  $p < 0.001$ ). Moreover, KYN and IDO levels were higher in mastocytosis patients with gastrointestinal symptoms compared to patients without digestive features (Figure 2.C-D;  $p = 0.01$  and  $0.045$  respectively).

### **Relationship between digestive features, tryptophan concentrations and IDO activity in mastocytosis.**

Patients with more intense abdominal pain (score  $> 5$ , on a scale from 0 to 10) tend to display minor TRP concentrations ( $p = 0.055$ ) and significant higher IDO activity ( $p = 0.04$ ). No other relationship was found between TRP level, IDO activity and other gastro-intestinal symptoms (Figure 2.E-F).

## **Discussion**

This is the first report studying TRP metabolism and the kynurenine pathway in mastocytosis with related GI symptoms. We found that mastocytosis patients displaying digestive features had higher IDO activity and decreased TRP levels as compared to healthy controls and to patients without digestive features. The decreased TRP level might be the consequence of an activation of the IDO pathway. This hypothesis is supported by the increased kynurenine level in mastocytosis patients with intestinal involvement. In these patients, IDO could be induced by the release of mast cell mediators in the digestive tract. Mast cells can secrete proinflammatory cytokines such as TNF alpha, interleukins 1 and 6, INF alpha (18) and are also able to express IDO (11). Moreover, recent work by Kawasaki showed that KYN catabolites are able to activate mast cells through an aryl hydrocarbon receptor which could stimulate IDO activity in mast cells, leading to kynurenine accumulation (19). The consequence could be a vicious circle activating more mast cells that, in turn, secrete proinflammatory cytokines leading to IDO activation.

Interestingly, gastro-intestinal lesions in mastocytosis patients could lead to an increase in intestinal permeability and circulating LPS which is known to stimulate proinflammatory cytokines and activate IDO, and thus the kynurenine formation (20).

Recent studies have focused on the role of tryptophan metabolism in irritable bowel syndrome (IBS). IBS patients share many features with mastocytosis patients displaying intestinal involvement, such as abdominal pain, bloating and infiltration by mast cells in the gut mucosa (21)(21)(21). Taken together, it is interesting to speculate that these two clinically close entities could share some pathogenenic aspects involving gut mucosal immune homeostasis possibly linked to the microbiota (21).

The presence of decreased TRP and 5-HT levels in mastocytosis patients could suggest a link to functional symptoms described by patients. Antihistaminics could be useful to prevent mast cell mediator liberation if they are specific for TPH1. Some authors have suggested the use of tryptophan hydroxylase inhibitors for irritable bowel syndrome which could be tried in digestive mastocytosis (22).

In conclusion, this study provides new elements in the pathogenesis of digestive features in mastocytosis which could open new therapeutic strategy in these patients as well as in gastrointestinal diseases such as IBS that share common pathogenenic aspects.

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## Figure legends

Figure 1. Schematic representation of tryptophan metabolism pathway

Cytokines (interleukines 1 and 6, TNF  $\alpha$ ) synthesized by activated mast cells in mastocytosis are able to induce the enzyme indoleamine-2,3-dioxygenase (IDO) that catabolizes TRP into KYN, thereby reducing the availability of TRP for 5-HT synthesis.

Figure 2. Tryptophan metabolism in Mastocytosis

Tryptase level (panel A), Tryptophan level (panel B), Kynurenine level (panel C) and IDO activity (panel D) in blood of mastocytosis patients with or without digestive symptoms and in healthy controls. Tryptophan level (panel E) and IDO activity (panel F) is associated with abdominal pain in mastocytosis patients with gastro-intestinal symptoms. \*,  $p < 0.05$ ; \*\*\*,  $p < 0.001$ . IDO activity is the result of the ratio KYN/TRP expressed in percentage.

Supplementary figure 1.

Examples of MC infiltration in the gastrointestinal tract. Panel A. Duodenal mucosa biopsy of a patient with mastocytosis showing a huge infiltration by round monomorphic cells suggesting mast cells (H&E x200). Panel B. Immunohistochemistry staining with anti-CD117 antibody showing large aggregates of mast cells in the lamina propria with diffuse expression of c-kit (CD117) antibody x200.

**Supplementary Table 1: Comparison of main features of mastocytosis patients with or without digestive symptoms.**

	<b>Digestive symptoms</b>	<b>No digestive symptoms</b>	<b>Healthy controls</b>	<b>p Digestive symptoms vs No digestive symptoms</b>
	<b>n = 26</b>	<b>n = 26</b>	<b>n=26</b>	
<b>Age at diagnosis (years) median (range)</b>	50 (25-65)	40 (26 – 71)	50 (25-65)	0.12
<b>Female/Male</b>	22/4	18/8	22/4	0.11
<b>WHO stage</b>				
<b>CM</b>	3	0	-	
<b>ISM</b>	19	23	-	0.3
<b>ASM</b>	3	2	-	
<b>SM-AHNMD</b>	1	1	-	



<b><i>KIT</i> mutation</b>				
<b>D816V</b>	21	24	-	0.22
<b>No (WT)</b>	5	2	-	
<b>Laboratory data, median (range)</b>				
<b>Tryptase (ng/L)</b>	27.2 (11.3 – 257)	30.5 (2.7 – 161)	4.35 (2.8-5.3)	0.7
<b>5-HT (nM)</b>	272 (34 – 1278)	226.5 (49 – 910)	352.5 (147-708)	0.09
<b>Tryptophan (µM)</b>	45.8 (22.2– 60)	46.2 (12.2 – 59.2)	52.4 (48.3-57.3)	0.6
<b>Kynurenine (µM)</b>	3.9 (1.9 – 5.3)	2.9 (1.6 – 4.6)	3.4 (1.9 – 4.7)	0.01
<b>IDO (%)</b>	8.7 (3.1 – 18.1)	6.65 (3.7 – 14.7)	6.16 (3.8-9.4)	0.04

Abbreviations: CM: cutaneous mastocytosis; ISM: indolent systemic mastocytosis; ASM:

aggressive systemic mastocytosis; AHNMD: associated clonal haematological non-MC-lineage

disease. 5-HT: serotonin; IDO: Indoleamine 2,3-dioxygenase;

<sup>1</sup>P was calculated according to chi squared Fisher's exact test or Mann-Whitney test.

Supplementary table 2. Main features of mastocytosis patients with digestive features

Patient number	Age	Sex	<i>KIT</i> sequencing	WHO stage	Serum Tryptase	Whole blood 5-HT	Plasma Tryptophan	IDO activity
1	54	F	D816V	ISM	18.5	219	47	9.2
2	25	F	D816V	SM-AHNMD	19	653	43	8.8
3	51	F	D816V	ASM	32	797	52	7.7
4	62	F	D816V	ISM	15.5	436	31.7	13.2
5	39	M	D816V	ISM	31.5	429	58	7.1
6	33	F	WT	ISM	15.6	173	47	10
7	57	F	D816V	ASM	37	226	49	9.4
8	51	M	D816V	ISM	48	665	44.5	9.7
9	39	F	D816V	ISM	68	1033	61	3.1
10	63	F	D816V	ISM	82	34	28	18
11	62	F	D816V	ISM	19	203	48	10.4
12	50	M	D816V	CM	13	152	49	6.5
13	50	F	WT	ISM	200	130	30	8
14	45	F	WT	ISM	15	1278	29	8.6
15	45	F	D816V	ISM	39	247	57	4.75

16	47	F	D816V	ISM	177	387	54.5	9.7
17	65	F	D816V	ISM	257	250	51	7.5
18	57	M	D816V	ISM	228	321	44	6.3
19	40	F	D816V	ISM	79	266	41	10.3
20	43	F	D816V	ISM	11.4	110	22	17.6
21	37	F	WT	ASM	95	192	60	4.3
22	38	F	D816V	ISM	21	278	34	8.6
23	54	F	WT	ISM	16.5	471	41.6	11.5
24	53	F	D816V	ISM	15	310	48	5.2
25	57	F	D816V	CM	23	240	45	7.4
26	43	F	D816V	CM	11	284	41	9

Supplementary table 3. Main features of mastocytosis patients without digestive features

Patient number	Age	Sex	KIT sequencing	WHO stage	Serum tryptase	Whole blood 5-HT	Plasma Tryptophan	IDO
1	37	F	D816V	ISM	5.5	233	40.5	7.65
2	31	F	D816V	ISM	3.8	374	48.6	5.35
3	60	F	D816V	ISM	22	95	12.2	14.7
4	34	F	WT	ASM	30	157	32.3	10.8
5	51	F	D816V	ISM	21.4	393	46.8	6.8
6	39	F	D816V	ISM	25	98	35.7	12.9
7	52	H	D816V	ISM	31	120	27.9	16.5
8	46	H	D816V	ASM	161	289	50	7.2
9	28	F	D816V	ISM	8.6	118	37.4	4.2
10	50	H	D816V	ISM	47.7	665	44.5	9.6
11	39	F	D816V	ISM	30	241	56.6	6.7
12	36	F	D816V	ISM	27	910	59.2	4
13	36	F	WT	ISM	40	105	44.8	6
14	44	F	D816V	ISM	90	221	56.8	4.75

15	32	F	D816V	ISM	19	335	50.2	5.6
16	66	H	D816V	ISM	35.6	85	45.7	6.6
17	71	H	D816V	ISM	43	199	49.6	5.3
18	42	H	D816V	ISM	47	404	56.7	3.7
19	48	F	D816V	ISM	37	128	40.2	6.2
20	26	H	D816V	ISM	57	49	47.6	6.7
21	55	F	D816V	ISM	80	338	39	4.8
22	38	H	D816V	ISM	45	232	49	5.9
23	41	F	D816V	ISM	6	156	57.4	4.5
24	62	H	D816V	SM- AHNMD	152	203	46.8	6.8
25	35	F	D816V	ISM	29	242	33.4	10.2
26	37	F	D816V	ISM	2.7	241	37	11.1