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► **To cite this version:**

Soraya Mezouar, Victor Morel, Laury Leveille, Noémie Resseguier, Céline Chartier, et al.. Progenitor mast cells and tryptase in Q fever. *Comparative Immunology, Microbiology and Infectious Diseases*, 2019, 64, pp.159-162. 10.1016/j.cimid.2019.03.011 . hal-02158738

HAL Id: hal-02158738

<https://amu.hal.science/hal-02158738>

Submitted on 22 Oct 2021

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Progenitor mast cells and tryptase in Q fever

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Abstract

Q fever is an infectious disease due to *Coxiella burnetii*. Following a primary-infection, *C. burnetii* may persist in some patients, leading to endocarditis and vascular infections. Mast cells (MCs), known for their role in allergic diseases, innate immunity and cardiac function, are produced by bone marrow, circulate as progenitors in the bloodstream and reach tissues for their maturation and activation. The latter may be estimated by measuring serum tryptase levels. We wondered if MC progenitors and tryptase were affected in Q fever. We showed a decrease in MC progenitor count in Q fever patients whereas serum tryptase levels were increased. ~~Interestingly, counts MC progenitors and levels of serum tryptase were correlated in Q fever patients with valvular lesions including Q fever endocarditis.~~ Taken together, our results show alterations of MC numbers and activity in Q fever patients, suggesting that MC are involved in Q fever pathophysiology.

Keywords: Mast cells progenitors, tryptase, Q fever, *Coxiella burnetii*, flow cytometry

60 **1. Introduction**

61 Q fever is an infectious disease due to the intracellular bacterium *Coxiella burnetii*.
62 Following primary-infection that is symptomatic in some patients, the infection may become
63 persistent in specific contexts such as immunodeficiency, valvulopathy or vascular disease.
64 The manifestations of persistent Q fever consist of endocarditis and vascular infections [1].
65 The evolution of Q fever is largely determined by anti-*C. burnetii* immune response [1]. This
66 latter consists of an inappropriate inflammatory response and decreased counts of
67 lymphocytes [2], monocytes [3], dendritic cells [4], and plasmacytoid dendritic cells in Q
68 fever patients [5]. It is likely that other innate immune cells including mast cells (MCs) are
69 involved in the pathophysiology of Q fever. MCs leave the bone marrow as progenitors, pass
70 through the bloodstream and complete their maturation in target tissues [6]. MCs are key
71 players in both inflammatory and immune responses, in addition to their well-known role
72 during immediate hypersensitivity reactions [7]. MCs also contribute to cardiac functions and
73 are involved in cardiovascular diseases [8]. Mast cell progenitors may be found in the
74 bloodstream and are identified as CD34⁺ cells expressing CD117 (c-kit) in association with
75 the high affinity immunoglobulin (Ig) E receptor (FcεRI) [9]. During infection, MC
76 progenitors are recruited to infected tissues where they mature and get activated, contributing
77 to host defense mechanisms against microorganisms [10]. The activation status of tissue MCs
78 can be estimated by the determination of serum baseline tryptase (sbT) [11]. *C. burnetii* has a
79 strong tropism for tissues rich in mast cells (MCs) such as adipose tissue [12], bone-marrow
80 [13,14] or lung [15]. However, the role of MCs in Q fever is unknown.

81 We wondered if MCs are involved in the pathophysiology of Q fever. The main
82 purpose of this study was to investigate the MC progenitor population in Q fever patients.
83 Using flow cytometry, we report here that circulating MC progenitors were decreased
84 whereas sbT was increased in Q fever patients compared to healthy donors. ~~We also reported~~
85 ~~a correlation between the decrease of circulating MC progenitors and the increase in sbT in Q~~
86 ~~fever patients with valvular disease.~~ Taken together, these results suggest a role of MCs in Q
87 fever pathophysiology.

88

89

90 **2. Materials and methods**

91 **2.1 Patients and controls**

92 We included 23 healthy blood donors and 22 patients with Q fever. Q fever patients belonged
93 to clinical subsets of acute (n = 10) and persistent Q fever (endocarditis group, n = 12). This
94 study was conducted with the approval of the Ethics Committee of Aix-Marseille University
95 and written consent of each patient. Patients consisted of 6 women and 16 men, median age
96 63, range 35 - 89 years. Controls consisted of 11 women and 12 men, median age 41, range
97 24 – 65 years. The diagnosis of acute and persistent Q fever was performed according to
98 recently updated criteria [1]. Briefly, patients with acute Q fever were diagnosed by the
99 presence of fever and/or hepatitis and/or pneumonia with serological criteria (IgG >200 and
100 IgM>50 against *C. burnetii* phase II or seroconversion) [1]. Persistent Q fever was diagnosed
101 on the presence of hepatitis, endocarditis or vascular infection and IgG >800 against *C.*
102 *burnetii* phase I. **As additional controls we included 15 patients with acute, non-Q fever,**
103 **native valve infective endocarditis.** Patients consisted of 6 women and 9 men, median age 61,
104 range 21 – 81 years. The diagnosis of acute infective endocarditis was performed according to
105 modified Duke criteria [16]. Valvular surgery was performed in all patients as valvular repair
106 or valvular replacement. A microbiological identification was obtained in all patients.
107 *Staphylococcus aureus* and *S. lugdunensis* were found in 4 and 1 patient respectively.
108 *Enterococcus faecalis* was found in 3 patients. *Streptococcus anginosus*, *S. mitis* and *S.*
109 *infarius* was respectively found in 1 patient. The other microorganisms recovered were
110 *Gemella sanguinis*, *Haemophilus influenzae*, *Escherichia coli* and *Bartonella quintana*.

111

112 **2.2 Cell isolation**

113 Blood was collected into EDTA tubes. Peripheral blood mononuclear cells (PBMCs) from
114 healthy donors and patients were isolated after centrifugation through Ficoll cushion and
115 suspended in RPMI 1640 containing 10% fetal calf serum, 100 U/ml penicillin and 100 µg/ml
116 streptomycin (Life Technologies, Courtaboeuf, France) as previously described [3].

117

118 **2.3 Serum baseline tryptase quantification**

119 Serum baseline tryptase levels were measured with the immunofluorescent enzyme assay for
120 α - and β -tryptase isoforms (ImmunoCAP, Thermo Fisher, Uppsala, Sweden).

121

122 **2.4 Flow cytometry**

123 Mast cell progenitors were identified by staining with anti-CD34 (Beckman Coulter, Nyon,
124 Switzerland), anti-CD117 (c-Kit receptor, CD117-APC, Beckman Coulter) and anti-IgE
125 (FcεRI, anti-IgE-PE, Bühlmann, Schönenbuch, Switzerland) antibodies (Abs). Cytometry
126 experiments were performed with a Canto II flow cytometer (Becton Dickinson, Le Pont de
127 Claix, France). Fifty thousand events were acquired and analyzed with FACS Diva software
128 (Becton Dickinson Bioscience).

129

130 **2.5 Statistical analysis**

131 Results were expressed as median and range. Statistical analysis was performed using the
132 Mann-Whitney *U* test. Adjusted *p*-values were provided in order to take into account the
133 multiplicity of comparisons within each analysis. The Benjamini and Hochberg method was
134 used, thus controlling the false discovery rate. Statistical significance threshold was set at $p <$
135 0.05.

136

137 3. Results

138 3.1 Circulating MC progenitors were specifically decreased in Q fever patients

139 The expression of CD117, surface IgE and CD34 was assessed by flow cytometry to identify
140 MC progenitors, as previously reported [9]. We found that approximately 1% of total PBMCs
141 were CD117⁺/IgE⁺, and 0.003 % were CD34⁺ MC progenitors ranging from 0.001 % to 0.012
142 % of total PBMCs (**Figure 1A**). Then we wondered if this subset of circulating cells was
143 modulated in Q fever. We found that the percentage of MC progenitors was significantly
144 decreased in patients with Q fever ($p = 0.001$) (**Figure 1B**) whereas no differences were
145 observed between acute and endocarditis group ($p = 0.8836$) (**Figure 1C**). In addition, the
146 percentage of MC progenitors was not altered in patients with bacterial infection other than *C.*
147 *burnetii* ($p = 0.1515$). These results showed that MC progenitors were specifically decreased
148 in Q fever patients independently of their clinical form.

149

150 3.2 Serum baseline tryptase was specifically increased in patient infected with *C. burnetii*

151 We therefore investigated sbT in Q fever patients. As depicted in **figure 2A**, sbT was higher
152 in Q fever patients than in controls ($6.18 \pm 2.87 \mu\text{g/L}$ versus 3.77 ± 1.85 , $p = 0.0448$).
153 Interestingly, compared to controls this increase is specifically found in Q fever patients
154 because other infections did not induce modification in sbT (**Figure 2A**). In addition, no
155 differences were observed in acute and endocarditis groups ($p = 0.4700$). These results
156 showed a specific increase of sbT in Q fever. ~~Moreover, we found a correlation between the~~
157 ~~number of MC progenitors and sbT levels in one subgroup of Q fever patients, namely in Q~~
158 ~~fever patients with valvular lesions including Q fever endocarditis ($R = 0.8240$, $p = 0.0034$)~~
159 ~~(**Figure 2B**).~~ These results suggested that this association was a marker of vascular
160 involvement in Q fever.

161

162 4. Discussion

163 In this study, we measured the frequency of MC precursors in blood from healthy
164 individuals and patients with Q fever. The identification was based on the assessment of the
165 co-expression of IgE, CD117 and CD34. This approach is necessary because each marker is
166 incompletely specific of MC progenitors. IgE expression identifies mostly MCs and
167 basophils, but monocytes from atopic patients can also bear surface IgE [17]. Although
168 CD117 is widely considered as a specific MC surface marker, it is also expressed by
169 basophils, myeloid dendritic cells, TCR α/β^+ T cells, B cells and NK cells [18]. We found that
170 MC progenitors represent a minor population in blood from healthy individuals. This is in
171 agreement with previous studies [6,9].

172 This study reported for the first time the decrease in circulating MC progenitors in Q fever
173 patients. This result has to be related to previous reports in which we found a decrease in
174 circulating lymphocytes [2], monocytes [3], dendritic cells [4] and plasmacytoid dendritic
175 cells counts [5]. While the decrease in circulating immune cells occurred mainly in Q fever
176 patients with endocarditis, here we did not observe differences in the number of MC
177 progenitors between acute and persistent Q fever. Decreased numbers of progenitors might be
178 due to impaired bone marrow production, or increased recruitment of progenitors into *C.*
179 *burnetii*-infected tissues. It has been reported that the numbers of MC increased in tissue-
180 specific due to the maturation of MC progenitors in human diseases [6,19]. Alternatively, the
181 decrease in MC progenitors may be due to their death. The interleukin (IL)-10 is known to
182 induce MC apoptosis [20] and is increased in persistent Q fever [21].

183 The second major observation was the increase in serum tryptase in patients with Q fever
184 independently of the clinical presentation. Circulating tryptase originates mainly from mature
185 MCs and in minute amounts from MC-committed progenitors [22]. Apart from acute MC
186 degranulation, which was not relevant for the patients included in this study, an increase in
187 tryptase levels has been reported in association with a poorer clinical condition or prognosis
188 in cardiovascular diseases [23]. ~~Indeed, in our hands, the increase in tryptase levels was~~
189 ~~correlated in Q fever patients with valvular lesions including Q endocarditis. This association~~
190 ~~is reminiscent of the abundant presence of MCs in cardiovascular tissues. The cardiac tropism~~
191 ~~of MC and the variation of the sbT is well documented in particular in cardiovascular diseases~~
192 ~~such as aortic stenosis and myocardial infarction [24,25].~~

193 In summary, we show that Q fever patients display less circulating MC progenitors but
194 higher levels of sbT. ~~The decrease in MC progenitors is correlated with sbT in Q fever~~

195 ~~patients with valvular lesions including endocarditis.~~ These results suggest MCs take part to
196 pathophysiology of Q fever.

197 **Acknowledgments**

198 We thank Dr. Christian Capo and Dr. Yassina Bechah for their help and advice during the
199 preparation of the manuscript.

200

201 **Formatting of funding sources**

202 Soraya Mezouar was supported by a “Fondation pour la Recherche Médicale” (FRM)
203 postdoctoral fellowship (SPF20151234951). This work was supported by the French
204 Government under the “Investissements d’avenir” (Investments for the Future) program
205 managed by the “Agence Nationale de la Recherche” (reference: Méditerranée Infection 10-
206 IAHU-03).

207

208 **Author contributions**

209 S.M and J.V conceived and designed the experiments. S.M, V.M, C.C and L.L performed
210 experiments and analyzed the data. N.R performed statistical analysis. S.M, D.R, J.L.M and
211 J.V wrote the paper.

212

213 **Declaration of interest**

214 The authors declare no competing interests.

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302

303 **Figure legend**

304

305 **Figure 1. Mast cell progenitors in Q fever disease**

306 PBMCs were recovered and analyzed by flow cytometry for the presence of MC progenitors
307 using CD34, CD117 and IgE fluorescent markers. (A) Representative graph of percentage of
308 cells expressing CD117, IgE and CD34. (B) The percentage of MC progenitors in PBMCs
309 from healthy donors and Q fever (C) acute or endocarditis patients is shown. The
310 nonparametric Mann-Whitney *U* test was used to compare control and patient groups.
311 Horizontal bar, median value.

312

313 **Figure 2. Serum basal tryptase in Q fever disease**

314 (A) The serum basal tryptase of Q fever patients was assessed in comparison to control and
315 other infections groups.

A.

