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To cite this version:

Anaïs Soares, Elise Fiaux, Martine Pestel-Caron, François Caron, Manuel Etienne. Bacterial persistence in biofilms: transcriptional analysis in a model of Pseudomonas catheter-assosciated urinary tract infections. IRIB, Jun 2015, Rouen, France. hal-02129794

HAL Id: hal-02129794
https://hal-normandie-univ.archives-ouvertes.fr/hal-02129794
Submitted on 15 May 2019

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Bacterial persistence in biofilms: transcriptional analysis in a model of *Pseudomonas* catheter-associated urinary tract infections

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**Background**

Biofilm (BF) is the main cause of antibiotic (ATB) failure during device-related infections. ATB failure might be related to persister (P) cells, a subset of bacteria able to survive to high ATB concentrations in BF, though tested fully susceptible (S) with usual minimum inhibitory concentration (MIC) tests in planktonic cultures. The aim was to develop in vitro a model of bacterial persistence to investigate the transcriptional adaptation induced by antibiotic stress.

**Methods**

**Catheter-associated urinary tract infection (CAUTI) model in vitro**
- A 4 days *Pseudomonas aeruginosa* (PA14) BF formed on urinary catheters (UC)
- 1h, 6h or 24h ciprofloxacin (CIP) exposure at different concentrations (from 1 to 2048xMIC)
- Surviving S and resistant (R) PA14 numbered on MH2 and MH2+CIP (1xMIC)

**Results**

**Impact of CIP exposure (Figure 1):**

- **Before CIP exposure:** 9 log_{10} CFU/ml including 6.6 log_{10} CFU/ml R cells, resistance mutation frequency = 5.10^{-3};
- **Biphasic curve after CIP exposure:**
  - initial and rapid 2 log_{10} CFU/ml drop of S and R cells in the same proportion plateau of bacterial populations despite increasing CIP concentrations;
- **Lower ATB doses to eradicate R cells than S cells** (768 to 1024xMIC vs 2048xMIC);
- **UC Sterilization at ATB concentrations > 1024xMIC** whatever the length of CIP exposure

Surviving S cells highly tolerant to ATB = Persister cells

**Selection window** of pure P population (Figure 2):

<table>
<thead>
<tr>
<th>CIP concentration (xMIC)</th>
<th>S cells</th>
<th>R cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>768xMIC (6h &amp; 24h)</td>
<td>[10^9]</td>
<td>[10^4]</td>
</tr>
<tr>
<td>1024xMIC</td>
<td>[10^6]</td>
<td>[10^2]</td>
</tr>
</tbody>
</table>

**Transcriptomic analysis (Table 1):**

In the conditions of CIP exposure associated with mixed R + P cells:
- no overexpression whatever CIP exposure

In the conditions of CIP exposure associated with P selection (as compared to untreated UC):
- *early (1h) intense upregulation for spoT, relA, rpoN and lasI (x10 to 35)*
- *fading upregulation over time (1h vs 24h) though more intense (x3 to 6) at higher CIP concentrations*

**Discussion**

- A catheter-associated urinary tract infection model in vitro for persister selection at very high CIP concentrations; ATB failure not related to R cells, but to P cells;
- Low RNA amounts extracted limiting the number of genes quantified;
- Early and intense activation of lasI potentially for BF consolidation, of relA and spoT for shutdown of cellular process, tolerance towards CIP and increased survival → multiple dynamic process of gene expression regulation leading to persister phénotype
- Overexpression of spoT controversial role → synthase or hydrolase activity to be determined

**Conclusion**

In this ATB-treated BF model of *Pseudomonas* infection, the transcriptional adaptation induced is highly dynamic and varies along the ATB exposure and according to BF environment. Eradication failure at high CIP doses was related to persister phenotype and associated with early intense upregulation of stringent response genes.