Human *ex vivo* and *in vivo* models for inflammasome activation

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**Background**  
Processing of pro-interleukin (IL)-1β and IL-18 is regulated by multiprotein complexes, known as inflammasomes. This process generates bioactive IL-1β and IL-18, two cytokines with potent pro-inflammatory effects. Increased IL-1β and IL-18 production and signaling are implied as key processes in the pathophysiology of various diseases ranging from autoimmune diseases (arthritis, atherosclerosis) to metabolic disorders (diabetes mellitus) and neurodegenerative disease (Alzheimer’s). Pharmacological control of IL-1β and IL-18 production is regarded to be a promising therapeutic approach.

**Aim**  
Development and characterization of human inflammasome challenges that may support the clinical development program of future investigational compounds suppressing inflammasome activity and/or IL-1β and IL-18 production.

**Methods**

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<th>Ex vivo experiments</th>
<th>Intravenous LPS challenge</th>
<th>Intradermal LPS challenge</th>
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<td>Healthy donors, blood cultures</td>
<td>Healthy volunteers</td>
<td>Healthy volunteers</td>
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<td>Incubation with LPS and ATP</td>
<td>IV LPS administration (2 ng/kg)</td>
<td>ID LPS administration (10 ng/injection)</td>
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<td>Cytokine release in culture supernatant</td>
<td>Circulating cytokines (blood)</td>
<td>Local cytokines (suction blister exudate)</td>
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**Results**

- **Figure 1:** Cytokine production upon *ex vivo* inflammasome challenge. Square: LPS, triangle: ATP, circle: LPS+ATP. X-axis: incubation time.
- **Figure 2:** Cytokine production after intravenous LPS challenge. X-axis: time after LPS administration.
- **Figure 3:** IL-18 production (top) and monocytes (bottom; HLADR+CD14+) after intradermal LPS challenge. X-axis: time after LPS administration.

**Discussion**

- LPS+ATP induces significant IL-1β and IL-18 production in fresh human whole blood cultures;
- Intravenously administered LPS induces a limited systemic IL-1β, but no IL-18 response;
- Intradermally administered LPS drives a robust local IL-1β response and enhances cellular influx;
- Conclusion: the *ex vivo* LPS+ATP challenge and the *in vivo* intradermal LPS challenge may be valuable models for future clinical trials investigating the effects of inflammasome/caspase inhibitors.