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MATERIAL-MEDIATED PYROGENS IN MEDICAL DEVICES

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OUTLINE

1. Introduction
2. Literature Search
3. MAT Assay
4. Conclusions

INTRODUCTION

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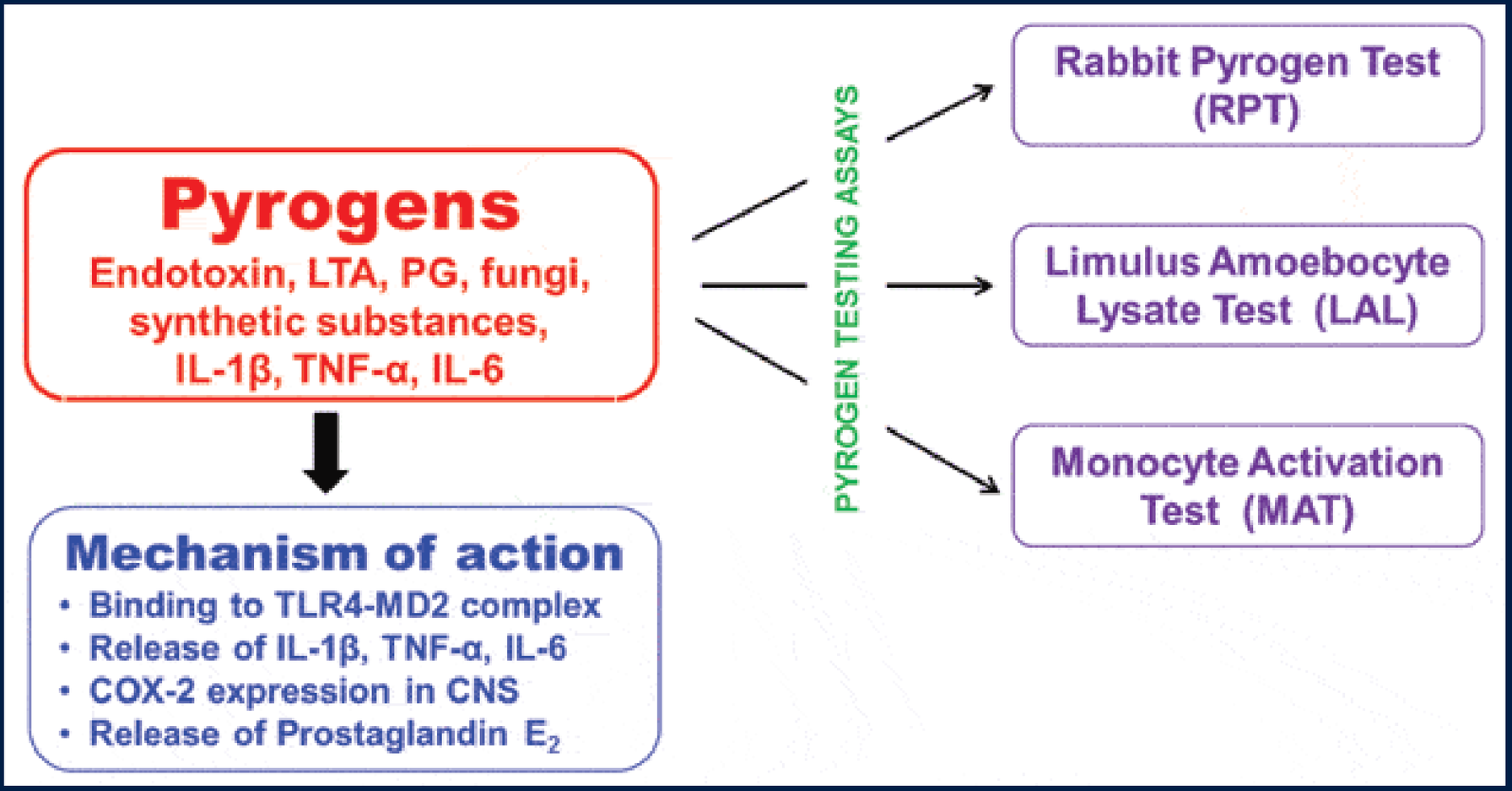
BACKGROUND

- Medical devices are screened for pyrogens.
- Exogenous pyrogens:
  - Endotoxin and Non-Endotoxin
- Current test methods:
  - Rabbit Pyrogen Test (RPT)
  - Limulus Amebocyte Lysate (LAL)
- Rabbits used for RPT testing:
  - 400,000 per year

PYROGEN TESTING ASSAYS



Ref: Singh et al., Applied Clinical Research, Clinical Trials and Regulatory Affairs, 2017

QUESTIONS

1. What is a “material-mediated” pyrogen (MMP)?
2. Are MMP’s found on medical devices?
3. What about the list of MMPs in ISO 10993-11:2017 Annex G?
4. Can the Monocyte Activation Test (MAT) detect MMPs?

LITERATURE SEARCH

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LITERATURE SEARCH

Material-mediated pyrogens in medical devices: Applicability of the in vitro Monocyte Activation Test.

Borton LK[1], Coleman KP[2].

⊕ Author information

Abstract

Pyrogenicity presents a challenge to clinicians, medical device manufactures, and regulators. A febrile response may be caused by endotoxin contamination, microbial components other than endotoxin, or chemical agents that generate a material-mediated pyrogenic response. While test methods for the assessment of endotoxin contamination and some microbial components other than endotoxin are well-established, material-mediated pyrogens remain elusively undefined. This review presents the findings of literature searches conducted to identify material-mediated pyrogens associated with medical devices. The in vivo rabbit pyrogen test (RPT) is considered to be the "gold standard" for medical device pyrogenicity testing, despite the fact that few medical device-derived material-mediated pyrogens are known. In line with global efforts to reduce the use of research animals, an in vitro monocyte activation test (MAT) has the potential to replace the RPT. The MAT is used to detect substances that activate human monocytes to release cytokines. This review will also describe the potential opportunities and challenges associated with MAT adoption for the detection of material-mediated pyrogens in medical device testing.

ALTEX
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LITERATURE SEARCH METHODS

- Review of English-language peer-reviewed journals, government documents, and committee-drafted standards.

- Selection criteria for inclusion required the study to address:
  - Pyrogens listed in ISO 10993-11:2017 Annex G.
  - Any chemical or material eluting from a medical device that induces a febrile response (excluding endogenous pyrogens e.g. cytokines and prostaglandins, fungi, yeast, viruses, bacteria, and parasites).
  - Prevalence of MMP in medical-devices.
  - Ability of the RPT or MAT to detect MMP.

LITERATURE SEARCH FINDINGS

- What is the definition of an MMP?
  - Introduction*
- What evidence of MMP in medical devices?
  - Sections 3.3 and 4.3*
- Can the Monocyte Activation Test (MAT) detect MMP?
  - Sections 4.3 and 5*
- What are potential +/- controls for MMP detection?
  - Section 6.3*
- What are the pros/cons of RPT and MAT for MMP detection?
  - Section 6*

*ALTEX paper

WHAT IS AN MMP?

- No published definition of a “material-mediated” pyrogen.

- A formal MMP definition would promote consistency across test methods and among stakeholders.

- Proposed “MMP” definition:

  Any exogenous non-biological substance known to cause a febrile response. This definition excludes substances such as endogenous chemicals (i.e., cytokines and prostaglandins), fungi, yeast, viruses, bacteria, and parasites.

EVIDENCE OF MMP IN MEDICAL DEVICES?

ISO 10993-11, Annex G Pyrogens

- International Organization for Standardization (ISO) publishes the ISO 10993 standards for biocompatibility assessment of medical devices.
- These ISO standards require pyrogen testing.
- ISO 10993-11 lists substances thought to induce pyrogenicity, but does not include citations that provide evidence of their *in vivo* febrile response.

MMP IN MEDICAL DEVICES?

ISO 10993-11, Annex G Pyrogens

Pyrogenic Substances per Annex G	Number of Citations
Cytokines, Prostaglandins, Neurotransmitters	20+
Inducers: *Polyadenylic, polyuridylic, polybionosinic and polyribocytidylic acids*	3
Uncoupling agents of oxidative phosphorylation: *Picric Acid (Trinitrophenol), Dinitrophenol, 4, 6-dinitro-o-cresol*	2
N-phenyl-β-naphthylamine	None (0)
Aldo-α-naphthylamine	None (0)
Metals such as nickel salts	3
Nanoparticles	15+

- **These substances are rarely found in medical device materials or processing aides.**

EVIDENCE OF MMP IN MEDICAL DEVICES

Additional MMP Evidence

- **Lit search found no publications:**
  - **Identifying additional material-mediated pyrogens,**
  - **Defining MMP characteristics,**
  - **Confirming MMP biological mechanisms of action,**
  - **Describing the prevalence of material-mediated pyrogenicity in medical devices.**

- **Conclusion**:
  - **No publications directly link a chemical or material eluent from a medical device to a febrile response *in vivo.***
  - **However, medical devices must still be tested for MMP to gain regulatory approval.**

MONOCYTE ACTIVATION TEST

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CAN THE MAT DETECT ENDOTOXIN?

Endotoxin: MAT Outperforms LAL / RPT for Medical Devices

- **Examples:**
  - **Mazzotti et al., 2006 evaluated clinically-relevant titanium alloy aneurysm clips.**
  - **Mohanan et al., 2011 tested five gel materials in a head-to-head comparison of the RPT, LAL, and MAT methods.**
  - **Werner et al., 2009 compared MAT and LAL results for intraocular lenses contamination.**
- **Conclusion**:
  - **MAT detected endotoxin on surface of medical devices and was more sensitive than RPT and LAL.**

CAN THE MAT DETECT NON-ENDOTOXIN?

Non-Endotoxin: MAT Outperforms LAL / RPT

- **Examples:**
  - ✓ **Patients administered serum albumin reported fevers. The contaminated serum albumin passed both RPT and LAL assays as part of a standard lot-release program, but tested positive in the MAT.**
  - ✓ **An infusion solution produced a fever response in patients despite having passed the LAL assay during standard lot-release. A retest of the implicated lots showed positive MAT and negative RPT and LAL results.**
  - ✓ **A dialysis solution contaminated with peptidoglycan and a Gram-positive bacteria strain passed both RPT and LAL, but tested positive in the MAT.**

- **Conclusion**:
  - ✓ **MAT may better protect patients from non-endotoxin pyrogens than RPT and LAL. RPT and LAL are animal-based assays and may miss some human pyrogens.**

MAT COMPARED TO LAL & RPT

MAT Outperforms LAL / RPT for Medical Devices

Conclusion:

- **There is strong evidence that the MAT can detect a wide variety of exogenous, non-endotoxin pyrogens.**
- **MAT has outperformed the RPT in every head-to-head comparison regardless of pyrogen source.**
- **The human-based MAT assay may be more patient-protective.**

POSITIVE CONTROLS FOR MMP DETECTION IN MAT?

- Coating or impregnating biomaterials with known material-mediated pyrogenic chemicals could serve as positive controls for the MAT.
- ISO 10993-11 Annex G compounds such as Picric Acid, Dinitrophenol, 6-Dinitro-o-cresol, and Naphthylamines are systemic toxins or carcinogens and not suitable for use.
- To date, no *material-mediated* pyrogenic substances have been identified.
- Hence, no MMP positive controls for the MAT may exist.

PROS/CONS OF THE RPT AND MAT FOR MMP DETECTION?

RPT: Pros/Cons	MAT: Pros/Cons
Requires the use of rabbits.	Based on human whole blood and human cell lines.
Well-accepted by regulatory agencies for MMP detection.	No regulatory acceptance for MMP on medical devices.
Fails to detect some human pyrogens.	More false positives than RPT, but detects all known human pyrogens tested to-date.
No internal positive and negative controls.	Potential for internal positive and negative controls.
Pass/Fail qualitative assessment.	Quantitative assessment.

CONCLUSIONS

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BENEFITS/CHALLENGES OF RPT FOR MMP DETECTION

Benefits of RPT

- Long history of established use.
- Regulators accept results, despite shortcomings.

Challenges of RPT

- No formal validation study verifying that the RPT detects MMP.
- Qualitative results. No internal positive or negative controls.
- Physical characteristics of the rabbit and its surroundings can cause variability in RPT results.
- Relies on the use of solvents to extract pyrogens from a medical device's material or surface
- Passing results do NOT guarantee a pyrogen-free product!

BENEFITS/CHALLENGES OF THE MAT FOR MMP DETECTION

Benefits of MAT

- Based on human whole blood and human cell lines.
- No animals.
- Potential for internal positive and negative controls.
- Quantitative assessment.

Challenges of MAT

- More false positives than RPT.
- Requires regulatory acceptance for material-mediated pyrogen detection.

CONCLUSIONS

1. Definition for MMPs needed.
2. No publications found that link a chemical or material eluent from a medical device to a febrile response in vivo.
3. MAT outperformed the RPT in every head-to-head comparison regardless of pyrogen source.
4. The MAT is 100% animal-free, quantitative, and has internal positive/negative controls.

WHAT'S NEXT?

- **Decide if an MAT validation study is appropriate or necessary.**
- **Consult with ISO WG 16, FDA, et al. about study parameters.**
- **Identify positive (+) controls.**
- **Determine sample types.**
- **Recruit stakeholder labs to participate.**

THANK YOU

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