Mathematical modeling of autoimmune diseases: a systematic review and analysis for advancing therapeutic development

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Abstract

This work represents a comprehensive review of mathematical models developed for various autoimmune diseases (ADs), their structure, underlying data, and application in model-informed drug development.

Introduction

- Global increase in ADs prevalence aggravates the unmet needs for disease-modifying medicines.
- The complex pathogenesis and etiology of ADs challenge the development of new therapeutic agents.
- Mathematical modeling is an essential tool for efficient drug development, applied to address recurrent questions on optimal dosing strategy, patient population, biological targets, hypothesis generation, and more.

Methods

Search strategy

A two-part search query:

1. 184 disease-specific terms [1]
2. studies on mechanistic, physiologically based or quantitative systems pharmacological models

500 potentially relevant publications in PubMed

✓ Mathematical model
✓ Description of autoimmune-related processes at any level of generalization and organization

47 articles with model-based analyses

38 unique mechanistic models

Statistical analysis and data visualization were performed in R Statistics software (version 4.0.2).

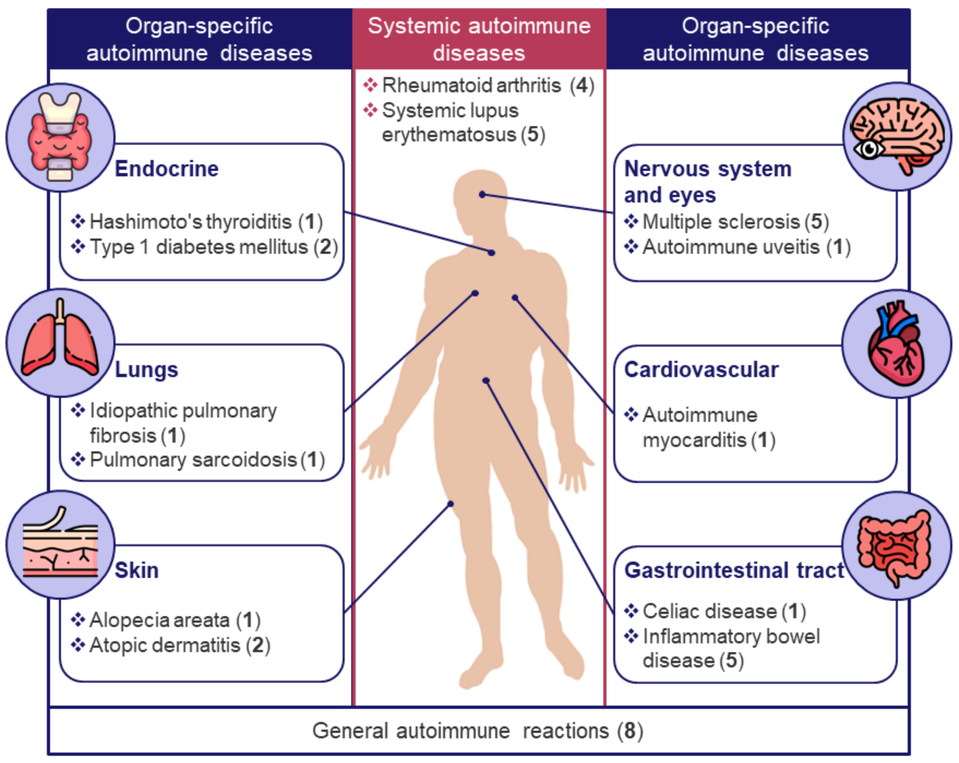
Conclusions

- Relatively small number of autoimmune indications (13 out of more than 100) are subjects of mathematical modeling.
- The majority of identified AD models were developed without extensive model calibration and evaluation, including identifiability analysis and external validation, and do not possess the capability for generating realistic patient populations, thereby limiting their quantitative predictability.
- The models were often developed in the absence of PK modules reflecting pharmacological intervention and did not incorporate clinical endpoints, further restricting their relevance for drug development.
- Among immunological components considered in the models, cytotoxic T-cells, B-cells and the elements of type I IFN pathway are the most underrepresented.
- The field of mechanistic models in ADs requires further efforts to proactively develop robust quantitative models that contribute to practical applications of mathematical modeling.

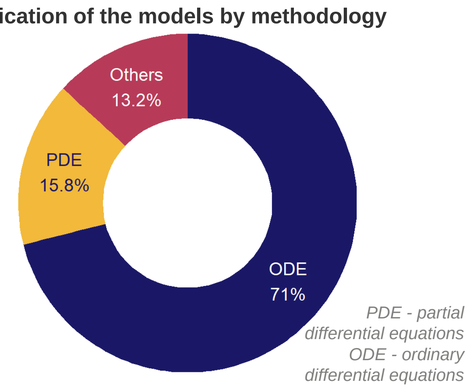
Results

Classification of the identified mathematical models

Classification of the models by target organ or system

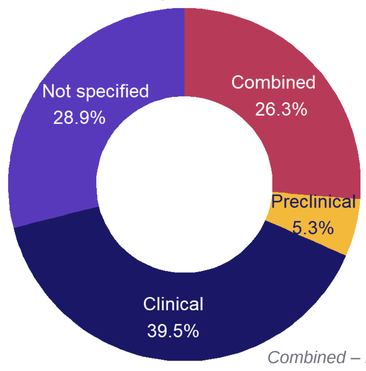


Classification of the models by methodology



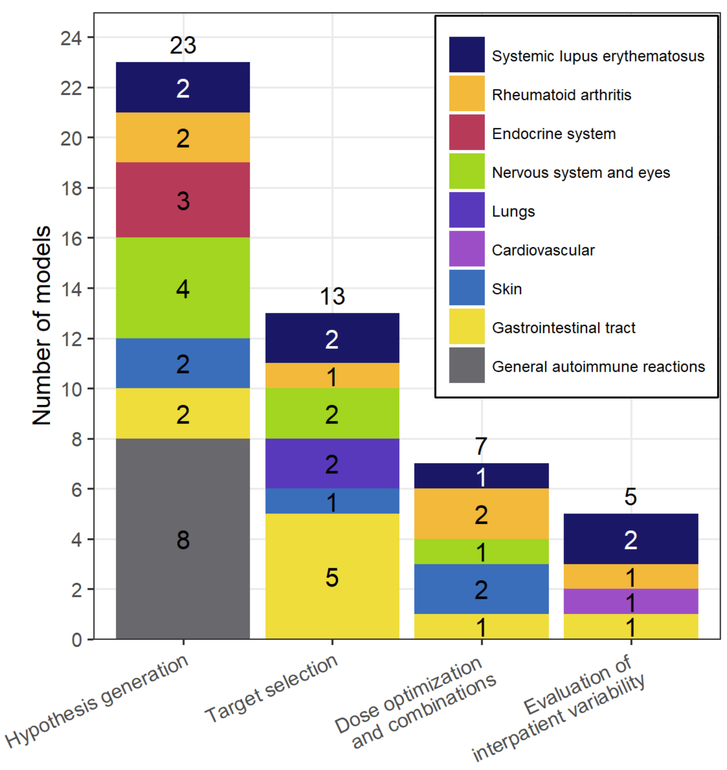
PDE - partial differential equations
ODE - ordinary differential equations

Classification of the models by the type of data used in their development and/or validation



Combined – both clinical and preclinical data

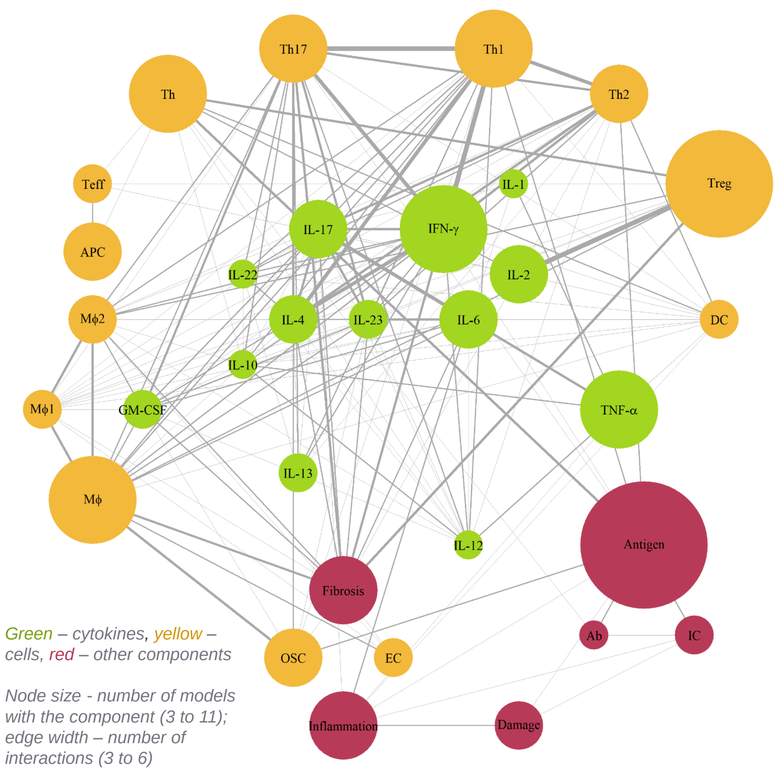
Classification of the models by application



- 38 mechanistic models across 13 systemic and organ-specific ADs were identified and characterized.
- More than a quarter of identified models lack various components of “good modeling workflow” [2, 3], such as rigorous parameter estimation, model qualification on clinical data, and validation based on external data, limiting their applicability to qualitative assessment of systems behavior, hypothesis generation and target selection.
- Most of the models do not contain pharmacokinetic (PK) modules based on existing compounds and operate with simplistic description of therapeutical interventions.
- The models proposed by Gao et al. [4], Nakada and Mager [5], Rogers et al. [6], and Miyano et al. [7] incorporate most of the good model development practices mentioned above as well as PK modules, enhancing the applicability of these models in model-informed drug development.
- Treatment-mediated response in clinical endpoints is considered only in one model [7].

Immunological entities embedded in the identified models

Network diagram of immune components represented in mechanistic models of ADs



Green – cytokines, yellow – cells, red – other components

Node size - number of models with the component (3 to 11); edge width – number of interactions (3 to 6)

- All variables were extracted from the modeling papers, resulting in 214 components. These components were then consolidated into 60 terms, and their simultaneous occurrences within models were calculated and added to the network diagram.
- One-third of the models describe antigen dynamics. Similarly, regulatory T-cells, which inhibit the activation and expansion of T-helper cells, cytotoxic T-cells and B-cells, are frequently modeled.
- The identified models extensively explored the interconnections between subtypes of T-helper cells (Th1, Th2, Th17) and cytokines (TNF-α, IL-1, IL-6, IL-17, IL-23, and IL-13).
- Immune elements such as cytotoxic T-cells, B-cells and type I interferon (IFN) pathway-related components, all involved in the development of multiple AD pathogenesis and targets of more recent therapeutics are underrepresented.

Ab-antibody; APC-antigen-presenting cells; DC-dendritic cells; EC-epithelial cells; GM-CSF-granulocyte-macrophage colony-stimulating factor; IC-immune complex; IFN-interferon; IL-interleukin; Mϕ-macrophages; OSC-organ-specific cells; Teff-effector T-cells; Th-T-helper cells; TNF-α-tumor necrosis factor-α; Treg-regulatory T-cells.

References

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