

INFLAMMATORY SIGNATURES IN EB

Scoping review

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EB – multisystemic disease

Complex interplay at the genetic, epigenetic, biochemical level
(inflammation, tissue remodeling,...)

Analyzing and reviewing the reported data on **immunological and inflammatory factors and mediators in EB** ...

- to gain a holistic understanding of **pathogenetic traits**
- to stratify and **categorize** EB (patients) based on immunological profile
- to **identify potential therapeutic targets**

SCOPING REVIEW

- ... tool to determine the scope or coverage of a body of literature on a given topic
- ... tool to **identify and map** the available evidence (overview)
- ... tool to identify **key characteristics** or **factors** related to a concept

5 main steps:

- **Identify** – What is the research question(s) - what domain needs to be explored?
- **Find** – locate relevant studies - electronic databases, conference proceedings, clinical trials, etc.
- **Select** – Choose studies that are relevant to the question(s) – use predetermined inclusion/exclusion criteria
- **Extract/chart** – organize the data from relevant studies selected
- **Collate** – Summarize and report the results

SYSTEMATIC REVIEW

- to **answer a particular question** addressing the feasibility, appropriateness, meaningfulness or effectiveness of a certain treatment or practice
- Includes assessment of bias / methodological limitations → **allows provision of implications for practice**
- PROSPERO registration of the review protocol required

Scoping review

Clarify key concepts/definitions in the literature

Identify and analyze knowledge gaps

Research question(s) often broad

Quantitative synthesis common

No risk of bias assessment

Systematic review

Confirm current practices / address variation or identify new practices

Produce statements to guide decision-making

Focused research question with narrow parameters

Synthesis more qualitative, and typically not quantitative

Mandatory critical appraisal (risk of bias assessment)

Both require: a priori review protocol; explicit/transparent/search strategy; standardized data extraction forms

Scoping review: Inflammatory signatures in EB

Objectives:

1. identify and summarize **inflammatory signatures** in patients with EB
2. describe and catalog identified molecular markers by clinical and preclinical research
3. analyze their associations with EB subtypes, symptoms, complications, and disease severity

Scoping review – research questions

Primary questions

- Which **molecular markers** have been found **dysregulated** (quantitatively, qualitatively) in EB patients that were functionally characterized (in vitro/in vivo) to imply a **pathogenic relevance** and potential therapeutic target?

Secondary questions

- Which **pathophysiological mechanisms** leading to elevation/decrease of molecular markers have been identified?
- How do the identified markers (e.g., elevation/decrease) relate to phenotype, severity, and outcomes of EB?

Eligibility criteria - Participants | Concept | Sources

- preclinical and clinical studies
- diagnosis of **EBS, JEB, DEB, KEB**
- treatment-naive subjects of any age, regardless of race, sex or severity

- only **human studies** (in vivo or in vitro)
- required to assess at least one molecular marker in vivo or in vitro

- 1991 onwards (after 1st EB classification consensus) | English full-text papers only
- exclusion of conference abstracts, meta-analyses, narrative and systematic review

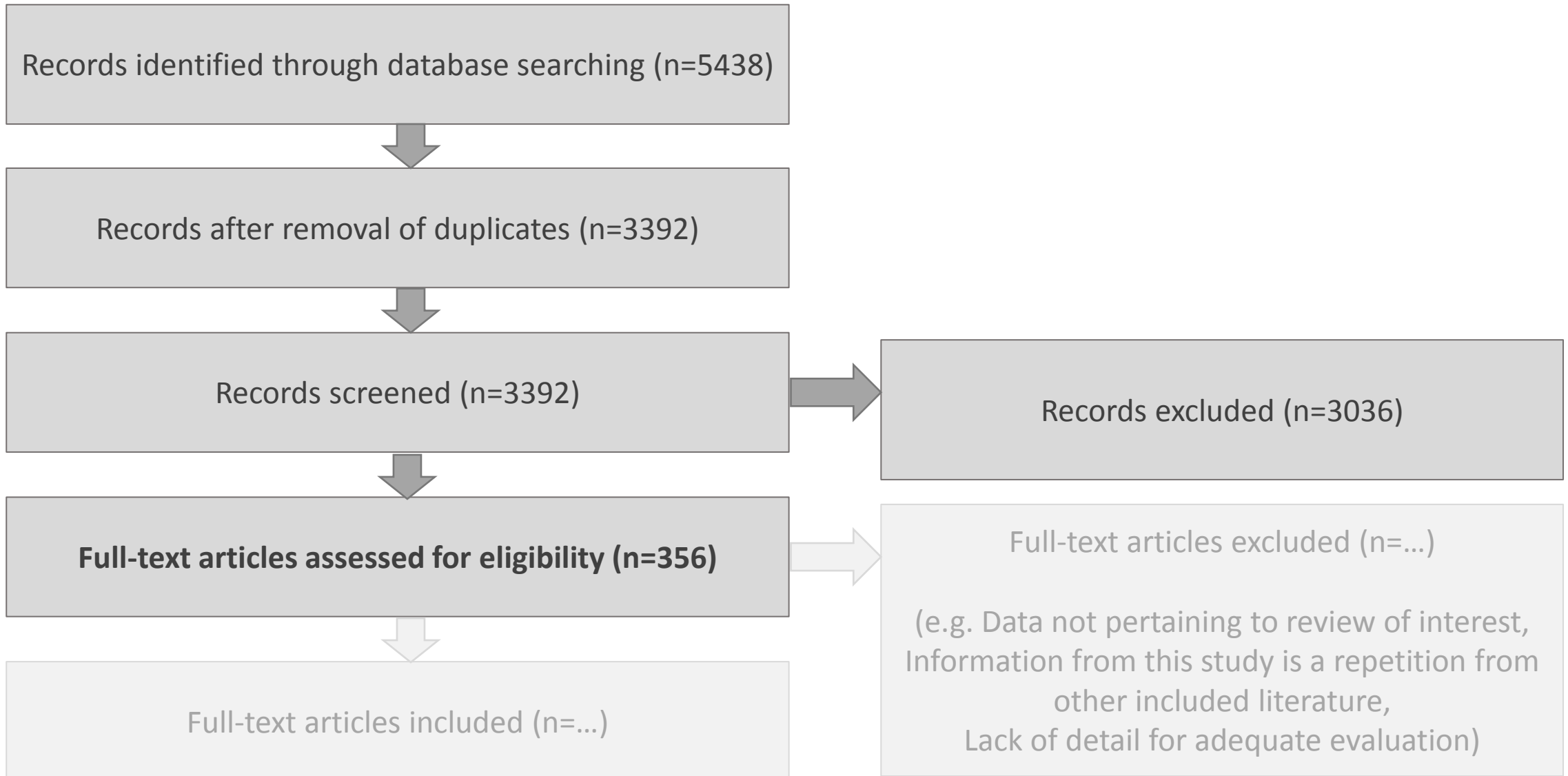
Search strategy

- 2 reviewers independently perform study selection
- Databases: PubMed | Medline (Ovid) | Cochrane Library (Ovid) | Web of Science | Google Scholar | Embase

Inflammatory mediators of interest:

proinflammat* or pro-inflammat* or cytokine* or neutrophil* or NK or cytotoxic or natural killer or chemokine* or CXCL* or SDF or CCL or CCR or CXCR* or interleukin* or Interleukin 6 or IL-1 or IL-6 or IL-8 or IL-4 or IL-5 or IL-9 or IL-10 or IL-12 or IL-13 or IL-17 or IL-33 or IL33 or IL1 or IL6 or IL8 or IL4 or IL5 or IL9 or IL10 or IL12 or IL13 or IL17 or alarmin or ST2 or lymphocyte* or Th1 or Th2 or Th22 or Th17 or CD4 or CD8 or Th9 or Treg or PD-1 or PD1 or MIF or TIM-3 or TGFβ or TGF-beta or TGF or tumor necrosis factor alpha or tnf-alpha or interferon* or INF-gamma or INF-γ or INFγ or MMP or matrix metalloproteinase* or TIMP or thymic stromal lymphopietin or tslp or BP180 or BP230 or DSG1 or DSG3 or immunoglobulin* or IgG or IgE or IgA or HMGB* or COX or p38 or FOXP3 or pi3k KLK or kallikrein or JNK or MAPK or ERK or MEK or mTOR or SMAD3 or growth factor or FGF or CSF or SGCF or EGF or EGFR or VEGF or HGF or NGF or PDGF or GMCSF or GM-CSF or hsp70 or cathepsin or CGRP or fetuin or meprin or iNOS or HIF-1 or ROS or FAAH or ANGPT or angiopoietin or TSP1 or thrombospondin or MIP or antimicrobial or macrophage* or mesenchymal stem cell* or mesenchymal* or fibroblast*

Progress...



Data extraction form

Topic
Date of charting
Reviewer initials
Authors
Year of publication
Origin/country of origin
Study features - Registration number
Study features - Citation/link to study
Study features - Title of study
Study features - Status
Study features - Sponsor and/or Collaborator
Study features - Countries of trial (per study location)
Study features – Type of study
Study features - Study Design - Phase
Study features - Study Design - Allocation
Study features - Study Design - Masking
Participants – diseases analyzed (also include studies investigating other diseases than EB with min 1 EB patient or subject?)
Participants – Enrollment (Nr. of total patients or subjects)
Participants – EBS (number)
Participants – JEB (number)
Participants – DEB (number)
Participants – Kindler EB (number)
Participants – Mean age (if human)
Participants - Age group (children vs adults)

Participants – Sex
Participants – symptoms (e.g. pain, itch)
Participants – complications (e.g. co-infection, tumor, pseudosyndactyly)
Participants – disease severity
Context - W/wo intervention (inflammatory analyses must be before intervention)
Context - Intervention - Treatment name
Context – Number of markers identified
Concept - Marker 1
Concept - Marker 1 - Name
Concept – Marker 1 – how often (no of patients or subjects) investigated in EBS
Concept - Marker 1 – Characteristics in EBS (Increased/decreased/present/unclear)
Concept – Marker 1 – how often (no of patients or subjects) investigated in JEB
Concept - Marker 1 – Characteristics in JEB (Increased/decreased/present/unclear)
Concept – Marker 1 – how often (no of patients or subjects) investigated in DEB
Concept - Marker 1 – Characteristics in DEB (Increased/decreased/present/unclear)
Concept – Marker 1 – how often (no of patients or subjects) investigated in KEB
Concept - Marker 1 – Characteristics in KEB (Increased/decreased/present/unclear)
Concept - Marker 1 – Domain (pathways involved)

Concept - Marker 1 – Key role in any pathway (e.g. JAK/Stat, PI3K/akt/mTOR, Ras/Raf/MAPK, JNF, MAPK/ERK, p38MAPK, WNT/b-catenin, NFkB,...)
Concept - Marker 1 – Downstream target of marker
Concept - Marker 1 – Downstream target of pathway
Concept – Marker 1 – Examined materials (e.g. skin, serum, blister fluid, cells (kernocytes/fibroblasts))
Concept – Marker 1 – location of material taken (e.g. lesional skin, non-lesional skin, mucosa, tumor tissue)
Concept - Marker 1 - Measurement instrument(s) (e.g. ELISA, Multiplex assay, bioassays, Flowcytometry)
Concept – Marker 1 – reason of change in EB
Concept – Marker 1 – experimental downregulation/upregulation Y/N
Concept – Marker 1 – change (up-/downregulation) leading to which molecular change
Concept – Marker 1 – change (up-/downregulation) leading to changes in proliferation, differentiation, orchestrated tissue repair, regeneration, orchestrated skin modelling/tissue genesis (in vitro, cell culture)
Concept – Marker 1 – change (up-/downregulation) leading to which clinical change
Concept Marker 1 – reported association between marker and complications (no/unclear/yes (which complication... e.g., co-infection, wound healing impairment, tumor, pseudosyndactyly))
Concept - Marker 1 – reported association between marker and symptoms (no/unclear/yes (which symptom... e.g. pain, itch))
Concept - Marker 1 – reported association between marker and disease severity (no/unclear/yes)

→ Narrative report

→ Tables, charts, graphs

Proposal: ERN Skin Delphi

- Data acquisition, mapping, identification of key factors > discussion, key messages, conclusions by **investigators**

Scoping review

- Critical appraisal & input by **network experts**
 - Significance, relevance, impact, innovation, therapeutic/target potential
 - Translatability, druggability/repurposing, feasibility

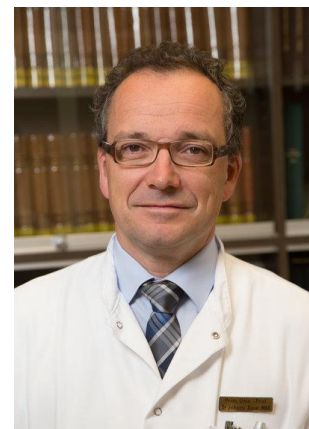
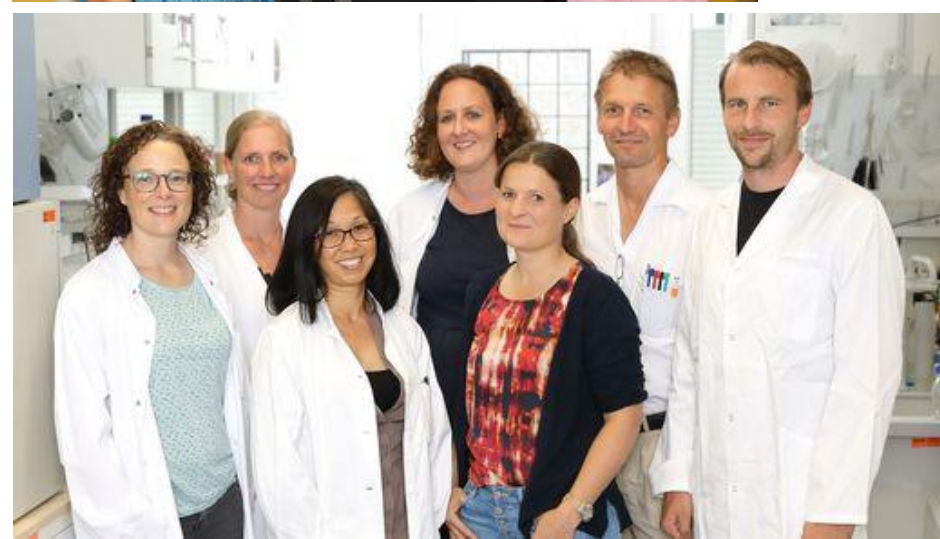


Questionnaire, e-Delphi

- Input consolidation & integration by **steering team**
- Consensus proposal
- Approval by network experts > **group consensus**



Consensus statement



The EB House Austria welcomes you!



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