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Eosinophil-Derived Transcript Signatures in Oesophageal Biopsies and Peripheral Blood from Patients with Eosinophilic Oesophagitis: A Review

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Abstract

Eosinophilic oesophagitis is diagnosed by counting eosinophils in a biopsy, which is a subjective measure of a patchy disease. Transcript profiling of the same tissue performs better than the count it is measured against. Blood, which would spare the endoscopy altogether, does not.

Objectives: *To review the published evidence on eosinophil-derived and epithelial transcript signatures in eosinophilic oesophagitis: what the oesophageal transcriptome contains, how a targeted molecular panel performs against histology, and how far peripheral blood markers track the tissue.*

Material and Methods: *Narrative review of transcriptome and expression profiling studies, molecular panel validations, biomarker correlation cohorts, consensus criteria and histology scoring studies indexed in PubMed and the major gastroenterology and allergy journals. Studies were eligible if they reported the accuracy of a molecular or blood marker against oesophageal histology in a defined population, or the reproducibility of the histological reference itself. No new patient data were generated; every estimate quoted is one published by the original investigators.*

Results: *Genome-wide profiling identified a transcript signature involving approximately one per cent of the human genome, conserved across sex, age and allergic status and distinct from non-eosinophilic chronic oesophagitis, with the eosinophil chemoattractant eotaxin-3 the most highly induced transcript. A targeted 96-gene panel derived from that signature identified adult and paediatric patients with approximately 96 per cent sensitivity and 98 per cent specificity across 194 validation samples, retained 96 per cent sensitivity and 100 per cent specificity on archival formalin-fixed material, and distinguished disease in remission from controls. In peripheral blood, absolute eosinophil count, eosinophil-derived neurotoxin and eotaxin-3 correlated with oesophageal eosinophil density at r = 0.56, 0.54 and 0.32 respectively, while eotaxin-1, eotaxin-2, interleukin 5 and faecal neurotoxin did not correlate at all.*

Conclusion: *The tissue transcriptome outperforms the eosinophil count that serves as its reference standard, and does so on the archival material most laboratories already hold. Blood markers rise in active disease but correlate only moderately with tissue, which makes them plausible for monitoring a known patient and inadequate for diagnosis.*

Abbreviations: *EoE – Eosinophilic Oesophagitis, EDP – EoE Diagnostic Panel, CCL26 – Chemokine (C-C Motif) Ligand 26 (Eotaxin-3), AEC – Absolute Eosinophil Count, EDN – Eosinophil-Derived Neurotoxin, eos/hpf – Eosinophils per High-Power Field, FFPE – Formalin-Fixed Paraffin-Embedded, qPCR – Quantitative Polymerase Chain Reaction, EoEHSS – EoE Histology Scoring System, PPI – Proton Pump Inhibitor, GORD – Gastro-Oesophageal Reflux Disease, IL – Interleukin.*

Keywords: *Eosinophilic Oesophagitis; Transcriptome; Eotaxin-3; Molecular Diagnosis; Blood Biomarkers*

Introduction

Eosinophilic oesophagitis is a chronic, immune-mediated disease of the oesophagus whose recorded incidence has risen steadily across population-based studies [1,2]. It is defined clinically by symptoms of oesophageal dysfunction and histologically by at least fifteen eosinophils per high-power field, a threshold carried through successive consensus documents [3,4,5,6,7].

That definition has two structural weaknesses. The disease is patchy, so a biopsy from one site may not represent the oesophagus [8], and counting eosinophils is a subjective exercise with imperfect agreement between pathologists [9,10]. A scoring system incorporating additional features was developed partly for that reason and has been reported to outperform the peak count itself [9,11].

Molecular profiling offered a different route. Genome-wide analysis of oesophageal tissue identified a conserved disease-specific transcript signature [12], which was subsequently condensed into a targeted diagnostic panel [8,13]. The attraction is objectivity: a transcript measurement does not depend on who is looking down the microscope.

A separate line of work has asked whether the same information is available in blood, which would remove the endoscopy from diagnosis and monitoring altogether [14,15]. This review sets out what the tissue transcriptome achieves, what the blood markers achieve, and why the two answers differ.

Material and Methods

Search strategy: PubMed and the archives of the major gastroenterology and allergy journals were searched for studies of molecular and blood markers in eosinophilic oesophagitis. Search terms combined eosinophilic oesophagitis with transcriptome, gene expression, diagnostic panel, eotaxin-3, CCL26, absolute eosinophil count, eosinophil-derived neurotoxin, histology scoring and diagnostic accuracy. Reference lists of retrieved consensus documents and panel validations were screened by hand.

Eligibility: Studies were included if they reported the accuracy of a molecular panel or blood marker against oesophageal histology in a defined population, the composition of the disease transcriptome, or the reproducibility of histological assessment. Consensus documents were included where they define the reference standard in current use. Paediatric and adult cohorts are both included and identified as such.

Data extraction and handling: Design, sample size, tissue or fluid sampled, platform, comparator and reported accuracy or correlation estimates were extracted as published. Correlation coefficients are reported rather than converted, and the reference standard is stated alongside every accuracy figure, because in this field the reference is itself imperfect. No pooling or re-analysis was performed and no patient-level data were obtained. Figures 1 to 3 and Tables 1 to 3 reproduce published values only. This is a narrative synthesis and was not registered as a systematic review.

Results

The disease has a conserved transcript signature: Genome-wide microarray analysis of oesophageal tissue identified a signature involving roughly one per cent of the human genome. It was remarkably conserved across sex, age and allergic status, and was distinct from the profile of non-eosinophilic chronic oesophagitis. The most highly induced transcript was CCL26, encoding the eosinophil-selective chemoattractant eotaxin-3, whose messenger RNA and protein levels correlated strongly with tissue eosinophilia and mastocytosis [12].

That the signature separates eosinophilic from other chronic oesophagitis is the point that matters diagnostically, because reflux disease is the principal differential and eosinophil counts alone do not reliably distinguish the two [16,17]. Earlier work had established the underlying T helper type 2 pattern of the inflammatory response [18,19,20].

A targeted panel outperforms the count it is measured against: The full transcriptome is impractical for routine use because of cost and turnaround, so a 96-gene quantitative polymerase chain reaction array with a dual clustering and dimensionality-reduction algorithm was derived from it. Developed on biopsies from 15 patients with disease and 14 controls, it was then applied to a separate cohort of 194 samples comprising 91 with active disease, 57 controls including patients in remission, 34 histologically ambiguous samples and 12 with reflux [13].

The panel identified adult and paediatric patients with approximately 96 per cent sensitivity and 98 per cent specificity. It distinguished patients in remission from controls, identified patients exposed to swallowed corticosteroids, and separated disease from reflux oesophagitis confirmed by pH-impedance testing (Figure 1) [13]. In a substudy of 45 randomly selected archival formalin-fixed samples it retained 96 per cent sensitivity and 100 per cent specificity against histology, with signature acquisition apparently unaffected across three years of archiving [13,21].

Two further properties matter more than the headline accuracy. Preliminary evidence suggested the panel could identify patients likely to relapse after treatment [13,21], and a later analysis found that it detected inflammation remote from the biopsy site without loss of sensitivity, which directly addresses the patchiness that undermines eosinophil counting [8].

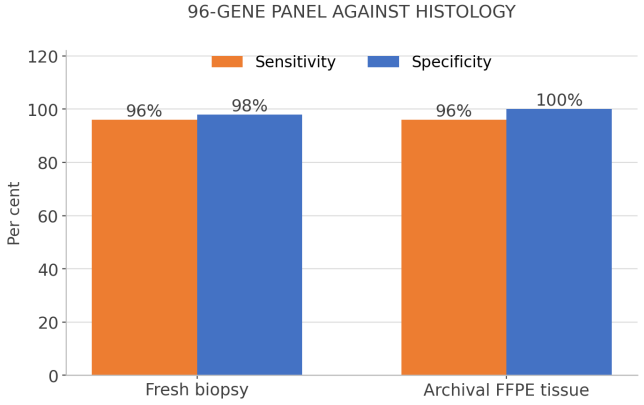

Figure 1: Accuracy of the 96-gene panel against histology on fresh and archival tissue [13]

Study	n	Material	Principal reported finding
Straumann et al. 2001 [18]	—	Tissue	Th2-type inflammatory response characterised
Blanchard et al. 2006 [12]	—	Tissue	Conserved signature; CCL26 most induced transcript
Konikoff et al. 2006 [14]	47	Blood	AEC and EDN correlate with tissue at r = 0.56 and 0.54
Wen et al. 2013 [13]	194	Tissue	96-gene panel, 96% sensitivity and 98% specificity
Collins et al. 2017 [9]	—	Tissue	Histology score outperforms peak eosinophil count
Dellon et al. 2018 [3]	Consensus	—	Updated diagnostic criteria; PPI reclassified as treatment

Table 1: Principal studies reviewed, with the material examined and the finding as reported by the original investigators

What blood delivers, and what it does not: A prospective cross-sectional study of 47 paediatric patients undergoing endoscopy measured peripheral blood absolute eosinophil count, eosinophil-derived neurotoxin, eotaxin-1, -2 and -3, and interleukin 5, together with faecal neurotoxin, and correlated each with oesophageal eosinophil density [14].

Three markers correlated: absolute eosinophil count at $r = 0.56$ ($p < 0.0001$), neurotoxin at $r = 0.54$ ($p < 0.0001$) and eotaxin-3 at $r = 0.32$ ($p = 0.04$) (Figure 2). Eotaxin-1, eotaxin-2, interleukin 5 and faecal neurotoxin did not correlate with tissue eosinophilia and were not raised in active disease [14]. All three of the positive markers were higher in active disease than in controls: absolute eosinophil

count 440 against 140 per microlitre, neurotoxin 50.3 against 31.1 nanograms per millilitre, and eotaxin-3 37.7 against 11.5 picograms per millilitre (Figure 3) [14].

The distinction to draw is between a marker that differs between groups and a marker that tracks an individual patient. A correlation of 0.56 explains under a third of the variance in tissue eosinophilia, so a blood result cannot substitute for the biopsy at diagnosis. The same figure is more defensible for following a patient whose diagnosis is already established, which is how the original investigators framed it [14,22].

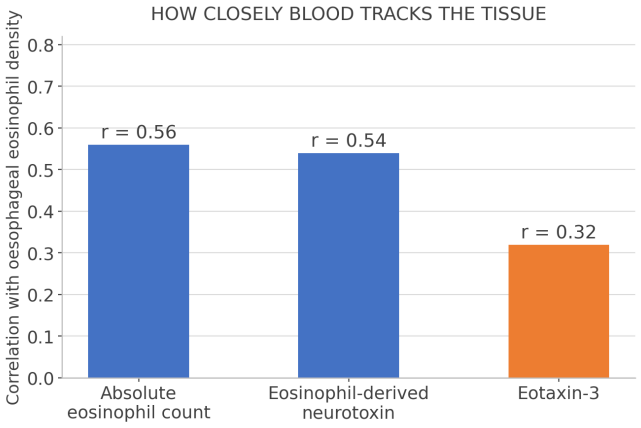

Figure 2: Correlation of blood markers with oesophageal eosinophil density in 47 patients [14]

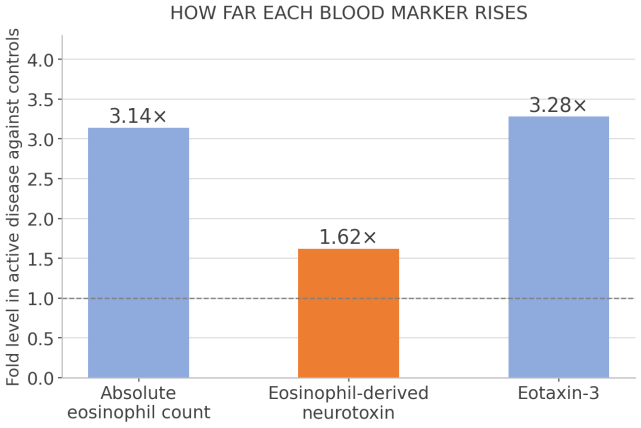

Figure 3: Level of each blood marker in active disease relative to controls, from the same cohort [14]

Compartment	What it measures	Reported performance and limitation
Oesophageal biopsy, histology	Peak eosinophil count per high-power field	The reference standard, but patchy and observer-dependent [8,9,10]
Oesophageal biopsy, transcript panel	Expression of 96 disease-associated genes	96% sensitivity, 98% specificity; works on archival tissue [13]
Peripheral blood	Eosinophil count and granule proteins	Correlates at r = 0.32 to 0.56; monitoring rather than diagnosis [14]

Table 2: What each compartment measures and how well it performs

The reference standard is part of the problem: Every accuracy figure above is measured against the eosinophil count, which is itself unreliable. Agreement between pathologists assessing the same biopsies is imperfect [10], and a validated scoring system incorporating basal zone hyperplasia, eosinophil abscesses, surface layering and other features was shown to outperform the peak count for both diagnosis and monitoring [9,11].

This creates an interpretive difficulty that is rarely stated. A molecular panel reported at 96 per cent sensitivity against an imperfect standard may be performing better than that figure suggests, since some of its apparent errors will be cases where the count was wrong. The 34 histologically ambiguous samples included in the validation cohort are precisely that group [13].

Marker	Correlates with tissue	Status
Absolute eosinophil count	r = 0.56	Best blood marker; monitoring only [14]
Eosinophil-derived neurotoxin	r = 0.54	Comparable to eosinophil count [14]
Eotaxin-3	r = 0.32	Weak in blood, dominant in tissue [12,14]
Eotaxin-1 and eotaxin-2	No correlation	Not raised in active disease [14]
Interleukin 5	No correlation	Not raised in active disease [14]
Faecal neurotoxin	No correlation	Not raised in active disease [14]

Table 3: Candidate blood and stool markers and their reported relationship to tissue eosinophilia [14]

Discussion

The striking result in this literature is that a transcript panel measured on the same biopsy outperforms the eosinophil count that defines the disease, and does so on archival material with no loss of accuracy [13]. That combination, better than the reference standard and compatible with tissue already in the block, is unusual. It also detects inflammation remote from the sampled site, which addresses the single most awkward feature of the histological diagnosis [8].

Blood is a different story and the title of this field invites the wrong inference. Absolute eosinophil count and eosinophil-derived neurotoxin do rise in active disease and do correlate with tissue eosinophilia, but at correlations near 0.55 they explain well under half the variance [14]. That is a monitoring signal in a patient whose diagnosis is settled, not a replacement for endoscopy in one whose diagnosis is not.

Why eotaxin-3 behaves differently in the two compartments

The most instructive detail is that CCL26 is the most highly induced transcript in oesophageal tissue [12] yet the weakest of the three correlating blood markers, at r = 0.32 [14]. A chemokine that acts locally to recruit eosinophils into the mucosa need not appear proportionally in the circulation, and the discrepancy is a reminder that a marker's importance in pathogenesis does not predict its usefulness in blood.

The same logic applies in reverse to interleukin 5, which is central to eosinophil biology and yet showed no correlation with tissue eosinophilia and no elevation in active disease in the cohort reviewed [14]. Mechanistic centrality and diagnostic utility are separate properties.

Study limitations

The limitations belong to the underlying literature. The blood marker data derive from a single cross-sectional cohort of 47 paediatric patients, so the correlation estimates carry wide uncertainty and may not transfer to adults [14]. The molecular panel was developed and validated by one group, and independent replication in other laboratories is limited [8,13,21]. Every accuracy figure is anchored to an eosinophil count of imperfect reproducibility, which biases

estimates in an unknown direction [9,10]. Diagnostic criteria changed materially in 2018 when proton pump inhibitor responsiveness was reclassified from a diagnostic criterion to a treatment [3,4,17], so studies published on either side of that change enrolled different populations. Treatment exposure alters both transcript and blood measurements, and cohorts differ in how much of it they permit [13,23].

Two gaps deserve naming. No study reviewed here compares the molecular panel against the validated histology score rather than against the peak count, which is the comparison that would establish whether the panel adds information beyond better-performed histology [9,13]. And no prospective study has tested whether monitoring by blood markers rather than by repeat endoscopy changes any patient outcome [14,22].

Conclusion

Eosinophilic oesophagitis has a conserved oesophageal transcript signature spanning about one per cent of the genome, with eotaxin-3 as its most induced component. A 96-gene panel drawn from that signature identifies the disease with roughly 96 per cent sensitivity and 98 per cent specificity, retains that accuracy on archival paraffin material, separates active disease from remission and from reflux, and detects inflammation the sampled biopsy missed. Peripheral blood markers rise in active disease but correlate with tissue eosinophilia only moderately, and eotaxin-3, the dominant transcript in tissue, is the weakest of them in blood. The tissue and the blood are answering different questions, and the evidence supports using the first for diagnosis and the second, at most, for follow-up.

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Conflict of Interest

None of the authors stands to gain from anything reported here.

Ethics Statement

What is reviewed here has all appeared in print before now. No patient was approached and no fresh data collected, placing the work outside the scope of ethical review.

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