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EDITORIAL

Potential relevance of type I interferon-related biomarkers for the management of polygenic autoimmune rheumatic diseases with childhood onset

Coziana Ciurtin[1]

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The substantial progress achieved in gene sequencing methods enabled rapid advances in genotypic and phenotypic characterisation of various autoimmune and autoinflammatory conditions spanning several medical specialties, with particular relevance for diseases with onset in early life, often linked to monogenic defects. Despite significant clinical heterogeneity, autoimmune rheumatic diseases (ARDs) share molecular pathways leading to chronic inflammation, which is reflected in the use of similar therapies across various clinical phenotypes, as well as across the lifespan.

The upregulation of type I interferon (IFN) pathway has been extensively investigated in "interferonopathies", inherited autoinflammatory conditions with early onset, characterised by dysregulation of homeostatic mechanisms of IFN-mediated immune responses [1]. The abnormal activation of antiviral sensors has been long recognised as the defining feature of inborn errors of autoimmunity associated with enhanced type I IFN signalling, such as the prototypical Aicardi-Goutières Syndrome (AGS) [2].

Serendipitous identification of autoimmune conditions triggered by IFN-based therapies [3] led to the investigation of shared pathogenic type I IFN signalling pathways between AGS and monogenic systemic lupus erythematosus (SLE) [4] and the discovery of novel SLE phenotypes associated with single gene defects [5, 6]. Familial phenotypes of early-onset refractory juvenile idiopathic arthritis (JIA), chilblain-like necrotising vasculitis, interstitial lung disease, or lipodystrophy have been also shown to be associated with type I IFN signalling defects [7], prompting clinicians to opt for genetic testing based on clinical suspicion. This is particularly relevant to management, as the majority of these conditions are refractory to conventional therapies [8], whilst there is emerging evidence of success of therapies targeting type I IFN pathway [9].

Type I IFN upregulation in polygenic ARDs

Although genetic testing is less relevant and not recommended for the diagnosis or management of ARDs with onset after the age of 5, as these conditions are considered to be largely polygenic, there is compelling evidence from research studies for the role of type I IFN pathway in the pathogenesis of ARDs in both children [10] and adults [11, 12]. Despite the lack of routine laboratory standardisation, different methods have been developed for measuring type I IFN signalling [10, 13, 14], as well as membrane-bound [15, 16] and soluble IFN protein levels [17, 18], or IFN-related chemokines [19] and functional assays [20].

Type I IFN production is cell-dependent, and various assays measure different aspects of IFN pathway downstream effects on cell-specific gene and protein expression, with various sensitivities and specificities, and variable technical challenges and availability, reflected in the lack of universal clinical validation of IFN-biomarkers across ARD phenotypes [21].

However, the most used technology for defining patients' "type I IFN signature" is based on the assessment of different sets of interferon-stimulated genes (ISGs) used to classify conditions associated with type I IFN dysregulation, from monogenic interferonopathies to SLE and dermatomyositis (DM). A set of six ISGs proposed by Yannick Crow and validated in IFN-driven monogenic diseases is frequently used to calculate the "IFN score" based on median fold changes of these genes and an established cut-off [10, 22].

There is emerging evidence for the role of type III IFN in ARDs. Although structurally different from type I IFNs and activating through different receptors, they share signalling

✉ Coziana Ciurtin
c.ciurtin@ucl.ac.uk

[1] Centre for Adolescent Rheumatology, Division of Medicine, University College London, Rayne Building, London WC1E 6JF, UK

pathways and have been shown to have meaningful clinical correlations in SLE [23], whilst data in childhood-onset ARDs are lacking.

Type I IFN upregulation in childhood and adult-onset ARDs

SLE and DM are two of the most investigated ARDs in terms of IFN signalling abnormalities across adult and childhood phenotypes. Studies found that at least a half up to 60–80% of adult-onset SLE patients had increased IFN signalling [24, 25], which was stable over time [24]. There are recognised ethnic differences, with non-White adult SLE patients with severe disease being characterised by 80–90% type I IFN activation [26, 27]. Less is known about childhood onset SLE (cSLE). Small European cSLE studies found that 82%, 57%, and 48% of patients had upregulated ISG expression, respectively [10, 28, 29], but investigated no clinical correlations. These lower rates could be explained by patients' ethnicity (predominantly white) and reasonably well controlled disease at inclusion.

Adults with DM had higher IFN scores than patients with SLE, rheumatoid arthritis (RA), or Sjogren's syndrome (SS) [30] and patients with juvenile dermatomyositis (JDM) had higher serum IFN-α levels (measured by Simoa technology) than SLE patients and comparable with monogenic type I interferonopathies [31], which supports the causative role of persistent type I IFN signalling in DM and JDM pathogenesis [31, 32].

The shared type I IFN pathway upregulation in ARDs is supported by good correlations found between IFN-α protein levels, functional activity, and ISG expression across various cohorts including both juvenile and adult ARD phenotypes [31], as well as concordance between increased peripheral blood and tissue IFN scores [33].

Type I IFN-related chemokines have been mainly studied in adult SLE, and they have shown good correlations with disease activity [19] and potential as flare prediction biomarkers [34]. In children with rare ARDs, type I IFN-related chemokines were upregulated during active disease, correlated with markers of endothelial dysfunction and did not completely normalise with treatment, aspects with potential implications for cardiovascular risk management [35], and disease risk stratification [36].

More interestingly, ISG upregulation in healthy young people was significantly influenced by sex determinants and pubertal status which can have implications for ARD risk. Healthy cis-females post-puberty had increased IFN-α production and enhanced ISG upregulation post IFN-α stimulation, which also correlated to the serum oestradiol levels [16], suggesting that stronger antiviral responses are sex-biassed and could predispose to abnormal type I IFN signalling. This is relevant to the strong female sex-bias observed across many ARDs with both post-pubertal and adult onset.

Clinical relevance of type I IFN upregulation in ARDs across age

Various studies investigated the clinical relevance of IFN signatures and highlighted their potential diagnostic and predictive value in SLE, RA, DM, SS, or systemic sclerosis with some limited research been conducted in the corresponding juvenile phenotypes, focused on cSLE and JDM [37]. It is important to recognise that some of these studies have not been validated across ethnically or geographically diverse cohorts and that they were likely affected by the lack of standardisation of various technologies used for measuring IFN signalling.

Upregulated type I IFN signalling pathway, from gene to protein expression, correlated with SLE disease activity, specific organ involvement, including arthritis, renal and skin disease, serological activity, and less time spent in low disease activity states [34, 38, 39]. In contrast, type I IFN signatures had no predictive value for disease activity trajectory over time in other cohorts [40]. Despite the paucity of studies in cSLE, there is evidence for positive correlations between increased serum IFN-α levels and disease activity, serological markers, and lack of treatment [41]. Contrary to the majority of adult SLE studies, type I IFN score did not correlate with the disease activity or serological markers in cSLE in a study which identified a unique clinical phenotype of cSLE characterised by low complement and dsDNA levels and high IFN score [42].

There is growing evidence for distinct phenotype and tissue IFN-related biomarker specificity in patients with polymyositis, DM, and JDM, as well as clinically relevant associations with poorer outcomes across age [12, 30, 43, 44]. Similarly, IFN-related biomarkers were associated with poorer lung prognosis in adults with systemic sclerosis [45] and distinct clinical phenotypes and lymphomagenesis risk in SS [17, 18], although data in children are lacking.

IFN signatures have also been proven useful as predictive biomarkers for SLE and RA disease progression in adults at risk [46, 47], and although no studies in children with pre-clinical disease are available, there is strong evidence for associations between gain of function genetic variants in the type I IFN pathway and autoimmune disease risk [2].

Potential implications of type I IFN-related biomarkers for the management of polygenic ARDs with childhood onset

Though advocating for IFN signalling testing in all young people with childhood onset ARDs is not justified, there is emerging evidence for the potential role of type I

IFN-related biomarkers for patient stratification with management implications.

Significant progress has been achieved with the licencing of the first type I IFN blockade agent (Anifrolumab) in SLE, based on successful clinical trials using IFN signature-driven patient stratification [48, 49]; this therapy is currently tested in cSLE. There is also evidence for the role of IFN-related biomarkers for identification of refractory JDM patients more likely to respond to JAK inhibition [50]. It is possible that the predictive value of type I IFN signatures found in adult studies could help identify cSLE patients more likely to respond to Belimumab [51] or benefit from conventional or targeted IFN therapy in systemic sclerosis with juvenile onset [45]. Further research into patient molecular stratification could provide the opportunity to explore the disconnection between the effect of hydroxychloroquine on decreasing IFN signalling and its lack of clinical benefit, as observed in adult SS [52].

The future investment should be focused on developing ultrasensitive and feasible assays for IFN-related biomarkers to facilitate the real-life assessment of their clinical utility compared to validated biomarkers. In the context of the rapidly expanding field of molecular diagnosis and personalised treatment approaches, one would expect that future research will prioritise the molecular characterisation of patients early in their disease course, with younger patients with childhood-onset ARDs being the main candidates. Childhood-onset ARDs are often more severe than the adult corresponding phenotypes, and patients have increased risk of exhausting all the available therapeutic options during their life course. IFN-related biomarkers relevant for many ARD phenotypes across age could potentially become cost-effective in supporting personalised selection of targeted therapies and tailored management strategies for specific organ involvement or comorbidity prevention early in life.

Compliance with ethical standards

Disclosures None.

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