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**The plasma proteome and prognosis for psychiatric symptoms in psychosis:
A focus on function, not factors**

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Psychotic disorders are debilitating and difficult to detect early when interventions could be most successful. The transition to psychosis encompasses a vaguely delineated subclinical interval during which positive and negative psychiatric symptoms or precursors emerge and persist. Effective tracking of this transition would benefit from biological markers that correspond to psychiatric symptom outcomes [1]. In psychiatry, biomarker development is uniquely challenging, because diagnoses derive from descriptive classifications of altered behaviors, not specific physiological functions [2]. In a recent paper published in *Brain, Behavior, and Immunity*, Byrne et al raise the bar for biomarker enquiries into psychosis with a novel investigation of the plasma proteome and its prognostic significance for behavior-based psychiatric symptoms [3]. What follows is a commentary regarding how tenuous linkages of biomarkers and behavioral outcomes are fortified with common-sense attention not on individual factors, but on functional surrogates representing whole pathway dysregulation.

At the forefront of this dialogue are two blood-based, multi-pathway systems, complement and coagulation. Originally described for immune and circulatory system roles, these pathways came under scrutiny when specific components portended biological associations with psychosis-related disorders, including complement *C4* gene risks in schizophrenia [1, 4, 5]. It seemed incongruent that peripheral pathways, not classically “psychiatric” in function, could be active in the central nervous system (CNS) and critical to healthy neuro-glial-development and maintenance. In this context, any pre-, peri-, or post-natal immune mis-queue is potentially contributing to phenotypic variations in neuroinflammation, synapse pruning and reorganization, cortical thickness, neuropil contraction, and dendritic spine densities [4, 6, 7].

The concept of co-regulated blood and CNS manifestations of a protein is enormously intriguing for biomarker enthusiasts. In practice, this redundant functionality can be difficult to capture, especially in oft-used shortcut analyses based on single proteins. Since both complement and coagulation comprise a diverse family of proteins, receptors, and regulators with interdependent functions, focus on individual factors may disguise dysfunction in broader functional pathways. Indeed, results from investigations of complement and coagulation in psychoses are inconsistently upregulated, downregulated or unchanged, even in previous excursions by Byrne et al [3]. But the team persevered, and what they did next was key.

In a large longitudinal cohort of 431 participants with clinical-high risk (CHR) for psychosis (North American Prodrome Longitudinal Studies 2 and 3 (NAPLS)), the team set aside a component-by-component analysis of complement and coagulation in favor of a whole pathway perspective. Over 30 plasma components were sorted according to intrinsic functions as complement activators, complement regulators, coagulation activators and coagulation regulators. For example, activator proteins included cascade amplifiers (C1R, C3, and F12), and regulators included pathway controllers and inhibitors (C4BPA, PROS1, and SERPING1) [3].

The group then focused the primary study outcome on negative psychiatric symptoms [3], poorly understood behaviors often preceding first episode of psychosis (FEP). Negative symptoms include social withdrawal, reduced verbal communication, blunted affect, and anhedonia [8]. In FEP, negative symptom severity can predict worse functional outcomes and increased risk of relapse [9]. While positive symptoms like hallucinations and delusions are manageable with antipsychotic medications, negative symptoms typically do not respond well. Although associations have been reported between proinflammatory cytokines and negative symptoms in FEP [10], relationships among complement, coagulation, inflammation and negative symptoms are less clear.

In the new study, negative symptoms (and positive symptoms for comparison) were measured using the Scale of Psychosis-Risk Symptoms at baseline and four follow-up visits over two years. Remarkably, complement and coagulation regulators but not activators, were prognostic for follow-up negative but not positive, symptoms, with this upregulation predictive of greater negative symptom severity. Variation in follow-up negative symptoms explained by complement and coagulation regulators was 1.6% and 1.1% respectively, a similar magnitude as depressive symptoms, positive symptoms, and global functioning. Prognostic associations with positive symptom outcomes were not detected, except very weakly for coagulation activators. Prognostic associations remained after adjustment for other clinical and demographic factors (including positive symptom scores, age, sex, antipsychotic use and exposure to cannabis) and sensitivity analyses [3].

Although complement and coagulation regulation was linked with negative symptoms, a role for underlying inflammation in CHR is tentative. If inflammation is what connects biology with behavior, it is surprising that pathway components classified as activators were not more directly prognostic. However, inflammation is heterogeneous, and complement and coagulation pathways are driven by sequential, enzyme-mediated amplifications of protein cascades, a hugely dynamic process. Pathway components active early may not be those captured later. Functional upregulations could reflect dysregulated chronic responses to prolonged, pro-inflammatory states even before CHR is identified. Indeed, plasma complement factor elevations in late childhood were found predictive of later psychotic-experiences [1]. Mechanistically, the failure to resolve complement and coagulation activation has neurodevelopmental implications and may lead to aberrant synaptic pruning in brain regions, such as the prefrontal cortex, which undergo synaptic refinement during adolescence to early adulthood time periods. If dysregulation coincides with early onset psychosis, worse negative symptoms may be expected. Alternative complement-modulated developmental trajectories can also be construed from absent connections between activating factors and negative symptoms. Complement proteins peak in childhood, whereas synchronised elevation of complement inhibitors coinciding with brain maturation occurs later in adolescence and young adulthood [11]. It may also be that regulatory factors are more reliable

proteomic measures, as studies demonstrate much variation in complement activators like C4, owing to age, sex, obesity, exposure to infections and autoimmune processes amongst others [12].

Traditional case-control, single molecule analyses are becoming diminishingly informative. As Byrne et al demonstrate, proof of pathway dysregulation can emerge through integrative approaches incorporating and stratifying multiple target proteins into functional groups (activators, regulators) [3]. With optimized multi-omic analyses coming to fruition, increasingly powerful bioinformatic and statistical examinations of interacting pathways in psychosis are following. Required will be acceptance that somatic comorbidities involving immune, gastrointestinal, and other anatomical and physiological systems in psychosis can provide mechanistic insight. Future cross-disciplinary biomarker forays could unveil novel, more intricate networks of intersecting genetic, lipidomic, metabolomic, molecular, proteomic, transcriptomic, and many other pathways, thus confirming the insufficiency of any diagnostic or therapeutic strategies not inclusive of a whole-body investigative approaches.

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