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Uncovering the unique properties of circulating proteasomes: A mass spectrometry perspective

Proteasomes are well-known mediators of intracellular proteostasis, yet their role in the extracellular space remains largely unexplored. Our recent study investigates the molecular architecture and functional specialization of freely circulating 20S proteasomes (c20S) in the bloodstream. Leveraging a CRISPR-engineered transgenic mouse model, we purified c20S complexes and applied a combination of native and top-down mass spectrometry to dissect their structural and compositional features. Our analyses revealed that serum proteasomes are predominantly uncapped 20S complexes, assembled intracellularly and exported to the blood. Native MS confirmed their intact assembly, while top-down MS identified a suite of post-translational modifications—including cysteinylation, glutathionylation, and truncations—that distinguish c20S from intracellular proteasomes. These extracellular complexes are enriched in immunoproteasome subunits and display enhanced caspase-like activity, indicating specialized roles in the blood environment. Together, these results showcase the power of integrative MS approaches in characterizing proteasome proteoforms and underscore the unique biology of circulating proteasomes, with potential implications for diagnostics and extracellular proteostasis.

User consent

yes

Authors: Dr MORGENSTERN, David (The Nancy and Stephen Grand Israel NationalCenter for Personalized Medicine, Weizmann Institute of Science); Dr BEN-NISSAN, Gili (Department of Biomolecular Sciences, Weizmann Institute of Science); Dr ZITTLAU, Katharina (Department of Biomolecular Sciences, Weizmann Institute of Science); SHARON, Michal (Department of Biomolecular Sciences, Weizmann Institute of Science); Mr LEUSHKIN, Yegor (Department of Biomolecular Sciences, Weizmann Institute of Science)

Presenter: SHARON, Michal (Department of Biomolecular Sciences, Weizmann Institute of Science)

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