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Seminar L11- Laboratorija za biosintezo in biotransformacijo

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From Structure to Function: the SPRY Domaincontaining SOCS Box Proteins as Physiological Regulators of iNOS and Anti-Infective Drug Targets

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Povzetek seminarja

The SPRY domain-containing SOCS box family of proteins (SPSB1 - 4) contain a central SPRY domain and a C-terminal SOCS box. We have shown that SPSB1 and 2 are important physiological regulators of inducible nitric oxide synthase (iNOS). The latter produces NO in response to a variety of stimuli including pathogens and cytokines, and plays important roles in innate immunity, inflammation, and cancer.

SPSB1 and 2 are adaptor proteins in the E3 ubiquitin ligase complex that polyubiquitinates iNOS, resulting in its proteasomal degradation. SPSB2-deficient macrophages showed prolonged iNOS expression and significantly increased nitric oxide production. Small molecules that could inhibit the SPSB-iNOS interaction should prolong the intracellular lifetime of iNOS, and will not only be valuable research tools but may also have therapeutic applications in combating bacterial and parasitic infections. To develop such inhibitors, and to find molecules that bind to other possible protein binding sites on SPSB2, we have carried out fragment-based screening by NMR. Structure-based approaches, based on our recent crystal structures of SPSB-peptide complexes are also being pursued.

VLJUDNO VABLJENI!