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Nitric oxide synthases-from genes to function

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It has been 35 years since mammals were discovered to synthesize nitrogen oxides [1], and 30 years since NO was found to be our endogenous vasorelaxant [2–4]. Ongoing research on all things NO continues to expand and to capture the imaginations of a wide range of scientists and medical professionals. This is amply illustrated by the five reviews in this special section of the current issue of Nitric Oxide. These reviews cover important current aspects of NO in pharmacology (NOS inhibitor design), medical genetics (eNOS polymorphisms), evolution & diversity (NOS in plants), cell signaling (protein S-nitrosation) and enzyme structure-function (NOS protein dynamics and electron transfer).

In the first article of the series, Santolini et al. provide a comprehensive update on NO synthase-like proteins that are found in genomes of plant species, and how they may be related both among plant species and toward the NOS-like proteins found in other phyla that have not yet garnered much attention in the NO research field (such as metazoans and fungi). They point out a number of interesting facets: the prevalence of NOS-like genes to be found in green algae but not at all in terrestrial plants, and that there is a closer relationship between the NOS protein sequences of some organisms than would be expected based on the distance of their evolutionary relationship. The authors also utilize their extensive knowledge about animal NOS structure-function relationships to critically discuss the NOS-like proteins in plants with regard to their potential abilities to bind and utilize the key NOS substrates and cofactors, and in several cases their analysis suggests that some plant NOS may not function well as classic NO synthases, and so may function in non-canonical ways within the organism.

The second article of the series, Olivera-Paula et al. summarizes what we know about eNOS polymorphisms, and how well they are associated with changes in eNOS enzyme expression, function, and regulation, and with the presence of cardiovascular diseases and/or treatment outcomes. Disorders covered include hypertension, obesity, preeclampsia, erectile dysfunction, and diabetes. When data is available, they also discuss how the single and combined polymorphisms, via haplotype analysis, impact measured biomarkers such as plasma nitrite/nitrate concentrations in subjects, and impact measured response outcomes to pharmacological interventions. Together, the review provides a convenient and up-to date framework to understand the global impact of eNOS polymorphisms and disease risks.

The third article by Wynia-Smith and Smith focuses on how an important NO-related post-translational modification, protein cysteine S-nitrosation, could serve in cellular signaling cascades. The authors review several facets, including the proposed chemical and protein-

based mechanisms of S-nitrosation or *trans*-nitrosation. In particular, they consider mechanisms that may enable specificity of protein S-nitrosation, and review newer evidence on how NOS co-localization with target proteins, NOS interactions with protein partners involved in *trans*-nitrosation, and specific protein sequence motifs in protein targets all may help to direct specific S-nitrosation events, and so enable biologic signaling by this process.

The fourth article in the series, Hedison et al. takes us into the realm of the NOS enzymes, discussing how their protein molecular motions are controlled and may relate to NO biosynthesis. The authors review the several approaches scientists are using to investigate NOS conformational populations and domain motions, and particularly they review how these aspects can be followed in real time and in conjunction with or in response to NOS electron transfer events, to look for fundamental connections between them. The review also touches on investigations done with related enzymes, and thus provides valuable comparison and contrast.

Finally, in the fifth article of the series, Poulos and Li update us on new developments in specific inhibitor design against the three mammalian NOS as well as against the bacterial NOS-like enzymes that enable virulence in several pathogens. Despite the persistent challenges in achieving isoform specificity, the authors show that more recent advances using protein/small molecule structure and dynamics modeling has opened up new pathways toward rational inhibitor design, and they review the results obtained so far with first-generation NOS inhibitor candidates discovered from such approaches.

In summary, this series provides a valuable snapshot of current topics pertaining to nitric oxide, and the articles are intended to enlighten current discussions on diverse aspects from protein to disease. We hope you find them informative and stimulating.

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