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FeS 2015, an IUBMB Symposium Gathering new information on the oldest cofactors in biology

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Foreword

Iron-sulfur (FeS) structures formed for the first time in the bottom of the primordial Ocean, where sulfide from the precursors of today's "black smokers" met iron in an acidic and anaerobic environment much different from today's deep sea. The surface of these structure has been hypothesized as the place where the earliest steps towards "biological chemistry" first evolved [1,2]. The versatility and stability of these structures has allowed them to survive through billions of years of evolution and, most notably, through the change from the primordial "anaerobic" Earth to an oxygen-rich environment. Incorporation of these structures in proteins has been exploited by evolution for functions as diverse as electron transport, nitrogen fixation and hydrogen evolution, redox and micronutrient sensing, DNA synthesis and repair, and many others, as seen in what follows. Indeed, as pointed out by some of the forefathers in this field, the diversity of structure and functions among FeS proteins is likely unmatched in biology [3].

This type of meeting has been held on a once-every two years basis since 2001, alternating locations on both sides of the Atlantic Ocean. Indeed, at the millennium turn, it had become evident that assembly of these structures was not the "spontaneous" process suggested by their ease of assembly "in vitro" [4-6]. Dedicated operons had been found just at that time, expressing an array of specific and dedicated proteins in various organisms and organelles [7-9]. These findings were scrutinized in that first meeting at Virginia Tech by a relatively small bunch of scientists, that included microbiologists, experts in various spectroscopic techniques, and bona-fide biochemists. Since then, much knowledge has been accumulated in this specific field, and new sectors of investigation have been opened, either as brainchildren of "old hands" or of their co-workers, as well as from much welcome newcomers that discovered new paths in the maze of interactions that contribute to this intriguing branch of science.

Countless reviews have appeared on these topics, including very recent ones appearing as special issues of highly popular Journals [10], but there is still room for old-fashioned person-to-person interaction, for introducing new faces and making new acquaintances, and for getting to the personal side of colleagues and competitors while enduring non-scientific activities. This is what occurred during FeS-2015 which was held in Bergamo in late June 2015, with support from IUBMB and from DeFENS/ University of Milan. The scientific committee of the Meeting placed a focus on structure-function relationships, as improvements in these aspects had been placed on the back burner in previous recent meetings, where the attention of the audience was placed on advances in our understanding of the contribution of the FeS biogenetic pathways to regulatory functions. However, ample room was left for these topics, as you may read in detail below or by exploring the conference website by yourself at http://www.ironsulfur2015.it/.

Highlights

The opening day (and the opening lecture, the night before) of the Symposium was dedicated to analyze the relevance of FeS proteins to human pathologies and to pathogenicity in bacteria relevant to human health and in common unicellular human parasites. There is indeed a growing awareness of inherited diseases (mostly linked to muscular functionality and energy supply) associated

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to malfunctioning of FeS biogenesis at various levels, as pinpointed by the invited speakers and by a conspicuous number of other presentations. In this frame, the much debated role of frataxin (an ubiquitous protein involved in the biogenesis of Friedrich's ataxia, undoubtedly the most common and the longest known myopathy) was the subject of a number of presentations. As pointed out in the opening lecture and by other speakers, FeS biogenesis is also crucial to the virulence and/or sensitivity to drugs of a number of common pathogens, and FeS proteins-based sensors are implied in regulation of specific functions in relevant human pathogens.

This new awareness of the central role played by FeS proteins as "environmental sensors" was looming in the background, also in other sessions, with particular reference to the ones dedicated to regulatory and sensing functions, where the role of various proteins involved in FeS biogenesis in various cellular compartments was scrutinized. Here, the emerging picture sees FeS proteins playing an increasing number of roles in the homeostasis of intracellular redox potential, with particular relevance in the case of regulating processes as diverse as sensing the chemical composition of the environment or the presence of potentially toxic species.

Along with these topics, the meeting also allowed attendants to gather new insights on the inner works of the machineries that allow to handle potentially dangerous chemicals (iron ions and sulfide are inherently toxic at amazingly low concentrations for most organisms). Specific proteins indeed take care of the "manufacturing" of the clusters suing a variety of tricks (and of ancillary proteins) to keep everything under control, and some previously obscure traits of these processes (such as the requirement for some sort of accompanying redox chemistry) begins to be clarified only now. Whether other metals may interfere with the "manufacturing" steps (either directly or through regulation of the expression/function of proteins thought to be essential) remains a matter of debate, as is the significance of regulatory interactions among the proteins in charge of the biosynthetic steps themselves.

Other proteins have been discussed as possibly taking part in the selective "delivery" of the products from the first manufacturing steps to "client" apoproteins. From the accompanying debate, it appeared that we just begun to understand the basics of the "logistics" of FeS delivery within and across the borders defined by intracellular membranes. This as of yet remains an unexplored territory primarily due to the methodological complexities of these studies, however it is one that holds high potential for interesting developments in the near future.

The same may be said when considering the role of FeS proteins in the biogenesis of molecules that contain sulfur, where some "shunt" of the FeS biosynthetic pathway may be operating alongside dedicated multi-protein assemblies. In this frame, some of the speakers also dealt with the biogenesis and functional aspects of multi-metal structures that share many common traits with Fe-only systems. These proteins contain clusters of daunting complexity, and are of outmost biotechnological significance, also with respect to the nowadays almost mandatory "sustainability" keyword.

Some aspects of the debate are reported in the following pages, that in most cases present novel contributions from young investigators that were awarded a money prize as recognition of their efforts. Prizes were made available by the International Union of Biochemistry and Molecular Biology (IUBMB), that has a long-standing policy of stimulating the active contribution of young researchers to scientific events. Other noteworthy contributions cannot be found here, because additional data are needed, because they have been submitted elsewhere, or because they represent hypothetical views built on results gathered through the years.

Finally, a presentation of the highlights of this scientific event needs to take into due account the remarks made by Dennis R. Dean at the end of the meeting. Prof. Dean originated this series of meetings almost fifteen years ago, and has been instrumental in helping the two of us in "setting the tune" also for the 2015 edition. In his brief - but intense - closing speech, he challenged the audience with a series of "what if" considerations, encouraging all of us to learn from the (recent) past in this field. On the basis of his own experience and of that of others, while listing a number of open issues in the whole area, he prompted the audience to avoid apparently obvious explanations, and to rethink what may seem already taken-for-granted. Thus, to use words from Primo Levi (a great Italian writer, and a chemist himself by trade [11]): "We are here for this — to make mistakes and to correct ourselves, to stand the blows and hand them out. We must never feel disarmed: nature is immense and complex, but it is not impermeable to the intelligence; we must circle around it, pierce and probe it, look for the opening or make it."

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