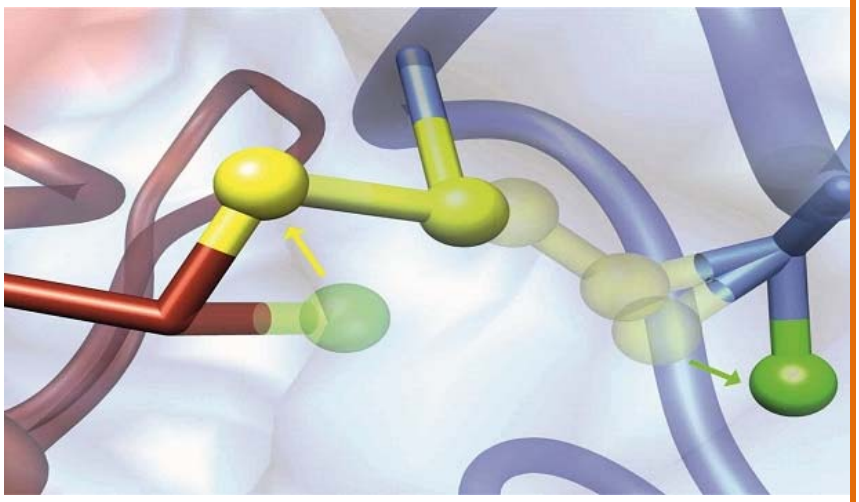
RESEARCH CONFERENCES



ESF-EMBO Conference

Thiol-based Redox switches in Life sciences

12-17 September 2015
Sant Feliu, Spain

Chaired by: Johannes Herrmann
http://redox.esf.org/

Highlights & Scientific Report

Conference Highlights

Please provide a brief summary of the conference and its highlights in non-specialist terms (especially for highly technical subjects) for communication and publicity purposes. (ca. 400-500 words)

Cysteine residues are highly reactive and can undergo multiple (oxidative) modifications. Multiple enzymes control the redox state of cysteine residues in vivo. Whereas the enzymatic properties of these factors were identified in the past, we are only beginning to understand the dynamic redox changes in the cellular proteome and its physiological consequences. In many cases, thiol oxidation controls the activity or stability of proteins and adapts them to physiological needs. In this respect, thiol modifications are similar in function and importance to other post-translational modifications. Owing to their short-lived nature and chemical diversity, the analysis of cysteine modifications however is very tricky. At this exciting conference, 43 scientific speakers plus 74 poster presenters reported about their recent (in most cases unpublished) results about the detection and identification of these modifications on many different proteins, about the enzymes which generate or remove these modifications and about their physiological consequences. Thereby, the scientists came from different fields such as molecular medicine, botany, structural biology, chemistry, physiology, oncology, genetics, parasitology and microbiology. Despite this broad multidisciplinarity, there was a vividly interactive and highly inspiring atmosphere at the conference and all participants focused on common biochemical aspects of thiol-based redox changes in proteins.

Exciting highlights at this meeting were insights in the role of thiol-switches for the development of cancer in humans (Christina Furdui, Wake Forest, USA), for the packaging and unpackaging of DNA in sperm cells (Benjamin Loppin, Lyon, France), for intracellular signalling (Rafael Radi, Montevideo, Uruguay), for the control of embryonic development (Elias Arner, Stockholm, Sweden), for the folding of secretory proteins in the ER (Neil Bulleid, Glasgow, UK; Carolyn Sevier, Cornell, USA; Marianne Koritzinsky, Toronto, Canada) or the regulation of mitochondrial protein biogenesis (Agnieszka Chacinska, Warzaw, Poland; Kostas Tokatlidis, Glasgow, UK; Jan Riemer, Cologne, Germany). Moreover, novel technical developments such as fluorescence-based redox probes (Tobias Dick, Heidelberg, Germany; Vsevolod Belousov, Moscow, Russia) or modifying chemicals (Kate Carroll, Miami, USA; Peter Nagy, Budapest, Hungary) were presented which will provide exciting innovative opportunities in the future.

All in all, this was a highly inspiring interactive conference which opened the door to new areas in the field and provided many opportunities for networking among the participants. At the business meeting, it was unanimously decided to organize a similar conference on the same topic in two years from now.

☒ I hereby authorise ESF – and the conference partners to use the information contained in the above section on 'Conference Highlights' in their communication on the scheme.

Scientific Report

Executive Summary

(2 pages max)

The general concept of thiol switches

Intracellular small-molecule-oxidants, the so-called reactive oxygen and nitrogen species have long been viewed as unwanted agents of 'oxidative stress' and 'oxidative damage'. Yet we currently experience a major change in perspective: These endogenous oxidants are increasingly recognized as second messengers in cellular signal transduction across all domains of life. These signals operate on responsive cysteine residues that serve as thiol switches. **A protein 'thiol switch' is defined as a thiol that is specifically and reversibly modified by oxidation, ultimately leading to a functional change in the respective protein.** Thus, a protein thiol switch is comparable to other posttranslational protein modifications such as phosphorylation/ dephosphorylation. Intriguingly, reversible modifications of cysteine residues may come in many different flavors, in particular disulfides (-S-S-), sulfenylations (S-OH), glutathionylations (-S-SG) nitrosylations (-SNO), and metal coordination (S-Zn, S-Fe), just to name the most prominent species. The possibility of interconversions between different modifications adds to the complexity of thiol switches (Figure 1).

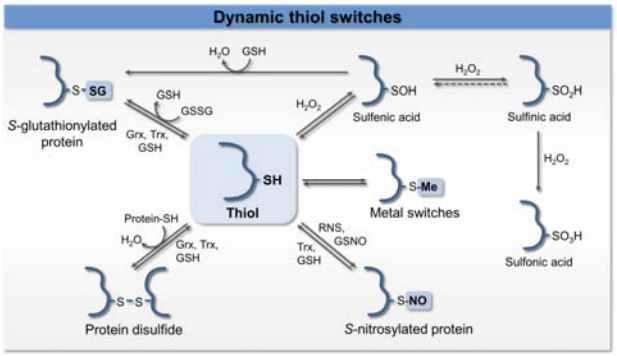


Figure 1. The most relevant protein thiol switches that were discussed at the conference.

There is increasing evidence for the importance of individual thiol switches in human health and disease, including immunity, neurodegeneration, cancer, cardiovascular disease, and inflammatory events. However, the underlying biochemical principles are still elusive. In particular, it remains unclear where the specificity for the thiol modifications comes from. In vivo, cysteine residues are modified selectively in a temporally and spatially controlled fashion. The underlying mechanisms that allow these selective switches to operate were intensively discussed at the conference.

The program was structured in way that the first talks concentrated mainly on basic principles (Session 1: New tools and technical developments; session 2: Model systems to study Redox switches; session 3: Structure and mechanisms of Redox machineries; session 4: Catalysis of Redox reaction). In the course of the meeting, the focus shifted more towards the larger picture and the physiological consequences and relevance of redox regulation was discussed (session 5: Cellular redox control; session 6: Cellular stress response; Session; 7 Redox biology in living systems). This structure proved to be very good as the initial talks provided a comprehensive overview and helped young researchers to understand the more complex talks in the subsequent sessions.

The speakers for invited talks as well as for short talks came from different research backgrounds (see above), were of different age (postdocs to senior professors), came from many different countries and were of mixed gender (46 % were female). Also the discussions were very lively and the poster sessions were extremely busy and continued long after midnight outside the conference hall after all doors were long locked.

No doubt about it, this conference was a highlight. There are a number of redox conferences (including two different Gordon Research Conferences). However, the ESF/EMBO meeting was fundamentally different to all other redox conferences in the respect that the focus was much more biochemical/structural with discussions centered on the molecular principles underlying thiol switch modulation. This mechanistic focus made this

conference unique and so successful.
Over the last few years many technical developments have changed the redox biology field tremendously. In particular mass spectrometry and the development of genetically encoded redox sensors allowed a temporal and spatial resolution of thiol modifications with chemical precision. However, all these methods are tricky and prone to lead to mis-interpretations if not done properly. This important technical challenge makes the meeting of redox biologists very important. The ESF/EMBO conferences in 2011 and 2015 were true networking hotspots where many contacts among collaborators were initiated or consolidated. There is no other conference series I attended over the previous years in which the interaction of participants was similarly vivid as at this redox conference. I heard from many colleagues that this conference and the previous conference in 2011 were the most useful, relevant and enjoyable conferences they had attended.

Forward Look

(1 page min.)

- *Assessment of the results*
- *Contribution to the future direction of the field – identification of issues in the 5-10 years timeframe*
- *Identification of emerging topics*

There was a very strong vote at the end of the conference for a next meeting in two years. Elena Hidalgo (Barcelona, Spain) was elected as the next organizer. She will try to raise money to make a next conference possible.

I expect that at the next conference, there will be an even stronger focus on the molecular structure of the redox switches in order to understand the mechanisms in great detail by which they are operated. Initially it was assumed that the reactivity (the redox-potential or the pKa value) of a given cysteine residue determines the probability of its oxidation. However, what we learned during the previous two conferences is that this is almost certainly wrong. At this conference there was a hypothesis proposed by Tobias Dick (Heidelberg, Germany) according to which highly reactive peroxidases serve as mediators which oxidize thiols in target proteins in a highly selective manner. This provocative hypothesis will presumably now be tested in many systems to evaluate its relevance in living systems. Studies in model systems such as yeast already indicate that this might be the main mechanism by which thiol switches are activated in the cytosol.

Moreover, there will be many systems biology approaches in which thiol modifications are followed in a proteome-wide manner in cells or even in entire organisms. It became obvious that redox switches are crucial for the development of organisms, and there is currently little understanding which proteins are relevant for this function.

Already this time we had a number of presentations on more applied aspects. Examples were talks on the relevance of thiol switches for the treatability of cancer or photoreceptor degradation-induced vision loss in humans, on the identification of drug targets against malaria or on successful strategies to increase the crop size in agriculture. These directions attracted much attention among the participants and were discussed vividly. In the next conference, we will therefore put an even stronger emphasis on applied aspects of redox biology.

- Is there a need for a foresight-type initiative?

Elena Hidalgo, Joris Messens, Katja Becker, Tobias Dick and I agreed to start the planning for the next conferences in the next weeks.

Business Meeting Outcomes

- *Election of the Organising Committee of the next conference*
- *Identified Topics*
- *Next Steps*

See above.

Atmosphere and Infrastructure

- *The reaction of the participants to the location and the organisation, including networking, and any other relevant comments*

There was a very positive feedback from the participants. I received many emails from colleagues and young scientists who all liked the conference very much. Of particular success were the elevator talks in which each poster presenter had one minute (!) to introduce him/herself and the main conclusion of the poster. This also "activated" many young scientists and improved their interaction, both scientifically and socially at the conference.

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