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Editorial

Redox regulation of differentiation and de-differentiation

Cell differentiation and the development of multicellular organisms are astonishing processes of self-assembly, controlled and driven by specific signaling molecules and signaling cascades including mechanisms of redox regulation, for instance, thiol switches and coupling to the redox state of nicotinamide dinucleotides.

Since the "great oxidation event" roughly 2.5 billion years ago organisms have to cope with oxygen and today the vast majority of all organisms depend on the availability of this element. But even 1.3 billion years before, in an atmosphere without oxygen, redox reactions may have provided the energy for the first metabolic steps in the evolution of life. The origin of life on earth may have been in cold [1] or hot environment [2], deep in the oceans [3] or on the top of volcanos [4]. Independent of this discussion, all these scenarios highlight the importance of redox processes for the origin and continuous evolution of life [3,5]. In particular, the FeS,H_2S/FeS_2 redox couple may have served as a source of energy as proposed by Wächtershäuse's theory of a chemoautotrophic origin of life [6]. In proteins of archaea the amount of iron is still extremely high, e.g. in *Ferroplasma acidiphilum* 86% of the proteins contain iron [7]. Interestingly, functions performed by FeS proteins in archea are often achieved by the nicotinamide dinucleotide couples NAD/NADH and NADP/NADPH in other organisms.

Today, redox modifications are increasingly recognized as important regulatory events in cellular functions, which has been highlighted, among others, in two former special issues of BBA-General Subjects, "Redox regulation of cellular functions" [8] and "Cellular functions of Glutathione" [9]. The aim of the present special issue was to compile a base of current knowledge regarding the roles of redox regulation in differentiation and de-differentiation. Some isolated reviews on different aspects of the topics have been published before, but the field is clearly lacking a state of the art compendium, bringing together the different concepts and comparing the similarities and differences between various cell types and species.

One of the first observations describing the important role of redox events during development and differentiation dates back to 1910 when Otto Warburg described oxidative events in eggs of see urchins [10]. The essential role of enzyme-catalyzed redox signaling events for development and differentiation became obvious when knock-out mice were generated targeting proteins from the thioredoxin (Trx) family of proteins, the master regulators of the protein thiol redox state. Lack of Trx1 [11] and 2 [12], their electron donors Trx reductases 1 [13] and 2 [14], as well as nucleoredoxin [15] in mice led to embryonic lethality or death shortly after birth. Zebrafish embryos with morpholino-targeted glutaredoxin 2 gene silencing display severe defects in development of both the cardiovascular system and the brain [16,17].

The dysregulation of redox signaling, "oxidative stress", has often been described as hallmark in the pathogenesis of various diseases. In particular, this is true for the de-differentiation of cells, i.e. cancer cell transformation, progression, and spreading. Therefore, dys- or deregulation of redox signaling is subject to numerous clinical investigations. However, also under these conditions, specificity and enzymatic catalysis of redox modifications have to be considered [18,19].

This special issue is arranged in four sections. Section A) focuses on (de)-differentiation of plants and symbionts and starts with a contribution by Ribeiro et al. describing "Redox regulation of differentiation in symbiotic nitrogen fixation" [20]. This contribution is followed by two articles on plant development focusing on thiol-based mechanisms [21] and ROS-mediated signaling [22]. Section A) is completed by a summary on "The imbalance of redox homeostasis in arthropod-induced plant galls: mechanisms of stress generation and dissipation", a pathogen-induced de-differentiation process in plants [23].

Section B) is dedicated to vertebrate differentiation. It consists of review articles by Wang et al. on redox regulation of stem cells [24], Hansen and Harris on the role of "glutathione during embryonic development" [25], and three articles focusing on the development or the remodeling of different organs: the brain [26], the heart [27] and the sperm [28]. Section C) describes cellular processes of differentiation and de-differentiation. Here, the impact of redox regulation on/by cytoskeletal dynamics [29], S-nitrosylation [30] and the ubiquitin–proteasome system [31] are summarized. This section is completed by Ye et al. on diseases directly connected to cellular differentiation [32]. The special issue is completed by a section addressing cancer, the most common de-differentiating disease. Foppoli et al. provide a timely overview on viral carcinogenesis [33], Jensen on the role of circadian rhythm on tumor cell de-differentiation using zebrafish as model organism [34] and Fernades and Gandin on "selenium compounds as therapeutic agents in cancer" [35].

This special issue covers several aspects of redox regulation of various differentiation and de-differentiation processes. Much is still unclear, however, we can expect a fast and exponential increase in the body of knowledge, foremost because of the availability of new tools, such as genetically encoded redox sensors [36] and quantitative redox proteomics [37]. We thank all authors, the referees, the executive editors of BBA-General Subjects, and the editorial office for their support that made this special issue possible.

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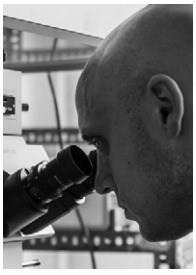

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