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Biomarkers of oxidative/nitrosative/carbonyl stress: How important are they and where to go in their analyses?

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Life in aerobic environments inevitably leads to the formation of reactive oxygen species (ROS). When in low concentrations, they are essential for redox signaling ("eutress"), and cell homeostasis. On the other hand, in higher concentrations, they can cause irreversible damage to macromolecules, leading to benefits (for instance, in cancer treatments, and as antibacterial or parasiticidal agents) or harm, in a process known as oxidative stress (OS) ("distress") [1]. Other species of strong relevance in this context are reactive nitrogen species (RNS), mixed reactive oxygen and nitrogen ones (RONS), reactive sulfur species (RSS) and reactive selenium species (RSeS) [1].

Oxidative stress, an imbalance between oxidants and antioxidants in favor of the oxidants, leading to a disruption of redox signaling and control and/or molecular damage [1], is the biochemical basis of aging and of a number of diseases, including cancer [2] and gastrointestinal [3], cardiometabolic [4] and neurodegenerative [5] diseases. In many cases, OS can lead to the increased formation of reactive carbonyl species (RCS), especially in conditions of high level of glycemia, which contribute greatly to the generation and aggravation of these diseases, giving rise to the term carbonyl stress (CS), related to various forms of metabolically generated aldehydes and electronically excited (triplet) carbonyls [1].

There is a strong connection between RONS, RCS and disease. This area is of increasing clinical interest and presents several scientific and technological challenges, including a detailed understanding of the link between OS and pathogenesis. The aim is to assess disease status and to develop preventive and therapeutic strategies in humans [1,6-8]. To achieve these goals, a series of biomarkers have been employed [6-8].

A single parameter as gold standard for defining redox status in clinical samples has not yet been reported [8]. In fact, the assessment of OS in clinical samples involves: (1) direct measurement of RONS levels, (2) detection of the resulting oxidative damage to biomolecules (RNA/DNA, lipids, sugars and proteins), and (3) the determination of antioxidant status (enzymatic antioxidant activities, nonenzymatic antioxidant levels or total antioxidant capacity) [8].

As representatives of approach (1), major analysed species are H_2O_2, HOCl, peroxynitrite and

others. In approach (2), principal biomarkers include: carbonylated proteins; advanced glycation end products (AGEs, derived from RCS); 3-nitrotyrosine; 3-chlorotyrosine; oxidized low-density lipoprotein (ox-LDL); other lipid oxidation products such as 4-hydroxy-nonenal (4-HE) and malondialdehyde (MDA); F2-isoprostanes; DNA/RNA oxidation products such as 8-oxo-deoxyguanosine; methionine sulfoxide and others. In approach (3), total thiols, glutathione reduced/oxidized ratio (GSH/GSSG) and cysteine/cystine redox couples, superoxide dismutase (SOD), catalase, glutathione peroxidase (GPx) activities, antioxidant index, measured through different methods, and several others have been used. The vast diversity in OS between diseases and conditions has to be taken into account when selecting the most appropriate biomarkers.

Despite the recognition of these biomarkers as being relevant for diagnosis, several drawbacks are still experienced in this area: the use of different biomarkers and protocols of analysis in the literature, revealing data fragmentation; and the measurement of biomarkers using nonspecific methods, as specific ones are too sophisticated or laborious for routine clinical use. There is a considerable data variability across laboratories. As such, no adequate comparison has yet been performed between different biomarkers and the methodologies used to measure them, making it difficult to conduct a conclusive analysis of findings from different laboratories.

Recommendations, critical evaluation and adaptation of proposed methodologies available in the literature are urgently required, to enable the investigators to choose the most suitable procedure for each chosen biomarker. Measurement of larger panels of biomarkers in key conditions will help to give a more comprehensive picture of their significance. In parallel with the exciting developments in ROS-validated targets and clinical indications, those markers and patterns that correlate best with treatment efficacy or mortality will eventually advance the field of ROS biomarkers.

Therefore, an integrative approach, with simultaneous multiple biomarkers' analysis, examining both pro- and antioxidant reactions, as shown before, will lead to a comprehensive score with higher sensitivity to physiological and pathological alterations.

The field is open for new methodologies and innovations, especially *in vivo* and in a non-invasive way, which require interdisciplinary knowledge in the search for selectivity, sensitivity and good analytical performance. The use in public health, for instance in point-of care devices, demands cheap assays, small sample amounts and portability, especially for *in situ* analysis. This arena will become the place where science meets technology, leading to evolution.

This is urgent, since the earlier diseases are discovered, the higher the chance of treatment and cure.

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