DNA damage assessment for precision medicine: an emerging diagnostic option

DNA damage analysis is an evolving diagnostic field, particularly for precision medicine, that opens new avenues for the use of potential biomarkers such as the phosphorylated histone 2Ax (γH2AX), 8-hydroxy-2'-deoxyguanosine (8-OHdG) or 8-oxo-7,8-dihydro-2'-deoxyguanosine (8-oxodG) (1-3). In fact, innovative diagnostic techniques have moved into the limelight that make it possible to analyze a plethora of new potential biomarkers, which requires the awareness of experts in laboratory medicine and beyond. Despite this enormous scientific progress, the number of novel biomarkers introduced into routine clinical diagnostics is still modest (4). In this focused issue, such a biomarker-based stratification of patients into cohorts with a distinct disease predisposition enabling early and targeted prevention or that benefit from a tailored therapy is discussed. Thus, Reddig *et al.* highlight the role of γH2AX as a promising marker for DNA double strand breaks (DSB) in the context of precision medicine in a comprehensive review (5). The authors compare γH2AX with other emerging biomarkers for genotoxicity analysis and review the different methods, characteristics, technical advances and potential clinical applications thereof. Obviously, one of the most intriguing changes has evolved in the field of precision cancer therapy. Though tumor heterogeneity is considered a major obstacle for precision medicine, much progress, nevertheless, has been achieved in treating cancer patients based on individual diagnostic profiles (6). In order to replace the traditional, uniform classification and treatment of tumor disorder, a paradigm shift seems to be taking place in which the high heterogeneity among tumors is addressed by a more comprehensive biomarker-based stratification of patients within the framework of precision medicine. Hence, Reddig *et al.* provide an overview of the applicability of genotoxicity methods in that context and underline the benefits of fluorescence microscopy with its superior sensitivity for γH2AX foci counting in the case of DSB assessment in a comparative analysis with other γH2AX-detecting methods (5,7). In another review, Ruhe *et al.* elaborate on 13 biomarkers including DNA repair response markers that have been described in the context of diagnostic tests, clinical studies or basic research of solid and hematological malignancies (8). In particular, the authors highlight markers of diffuse large B-cell lymphoma being one of the most aggressive forms of non-Hodgkin's lymphoma diagnosed in more than 50% of lymphoma patients over the age of 65 (9). They conclude that a broad range of biomarkers would be required to enable complete and early detection of oncological illnesses, which requires a multiplex diagnostic methodology.

The need for readily accessible patient material for such diagnostic approaches is addressed by Sowa *et al.*, who demonstrate the use of capillary peripheral blood mononuclear cells as a possible substrate for the automated detection of γH2AX foci (10). The authors underline the benefits of capillary puncture in contrast to venipuncture for the collection of blood specimens especially for pediatric and multi-morbid patients. Thus, this new approach could facilitate the planning of clinical trials or experimental settings.

As currently commonly accepted, automation and standardization are urgently required for the predominantly subjective genotoxicity tests, and the initiatives related to the later ones are discussed (5,11-13). The development of automated versions of these methodologies, especially with regard to the DSB analysis by γH2AX foci counting are major topics of this focused issue. The use of digital fluorescence and emerging Bioimage Informatics Tools are discussed in length by Schneider *et al.* in this context (14). The authors give an overview of open source image processing software packages such as the graphical user interfaces CellProfiler, Icy, ImageJ/Fiji and FindFoci which are widely used for γH2AX foci counting currently. Moreover, software packages such as CellProfiler and Icy that can obtain high-content information on biomarkers through multiparametric analyses, as well as R and Python are described using examples of custom-made solutions.

Apart from cancer, DNA damage analysis might be a useful diagnostic tool for metabolic illnesses. In this issue, Lippi *et al.* report an interesting example of physical exercise as an essential part in prevention and therapeutic management of subjects with type 1 and 2 diabetes mellitus (15). The authors investigated the burden of DNA injury after middle-distance endurance running in diabetic subjects and concluded that the extent of DNA damage in diabetics engaged in middle-distance running was not significantly different from that observed in euglycemic subjects. It is noteworthy that DNA damage analysis by γH2AX foci counting was reported as a useful marker for strenuous exercise recently (16).

Another set of biomarkers used for the assessment of oxidative stress leading to the accumulation of reactive oxygen species

(ROS) is discussed by Korkmaz *et al.* in this focused issue (17). It is a well-known fact that ROS can result in structural cellular and/or genetic changes modulating essential triggers of tumor formation, especially at the initial steps of carcinogenesis (18). Both 8-OHdG and 8-oxodG are the most frequently observed single nucleotide-base lesions and thus potential biomarkers of oxidative DNA damage (19). Novel techniques for 8-OHdG detection in the connection with oxidatively-generated clustered DNA lesions are emerging, enabling the application of automated image analysis at a single-cell level (17,20,21).

Altogether, advances in DNA damage analysis and the emergence of corresponding novel biomarkers is a rapidly developing field with great potential for its application in precision medicine (22). Laboratory experts can expect further progress in this area in the near future and should follow the upcoming achievements closely.

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References

1. Rothkamm K, Lobrich M. Misrepair of radiation-induced DNA double-strand breaks and its relevance for tumorigenesis and cancer treatment (review). Int J Oncol 2002;21:433-40.
2. Ivashkevich A, Redon CE, Nakamura AJ, et al. Use of the gamma-H2AX assay to monitor DNA damage and repair in translational cancer research. Cancer Lett 2012;327:123-33.
3. Yan S, Sorrell M, Berman Z. Functional interplay between ATM/ATR-mediated DNA damage response and DNA repair pathways in oxidative stress. Cell Mol Life Sci 2014;71:3951-67.
4. Lippi G, Plebani M. Personalized medicine: moving from simple theory to daily practice. Clin Chem Lab Med 2015;53:959-60.
5. Reddig A, Rübe CE, Rödiger S, et al. DNA damage assessment and potential applications in laboratory diagnostics and precision medicine. J Lab Precis Med 2018;3:31.
6. Cirkel GA, Gadellaa-van Hooijdonk CG, Koudijs MJ, et al. Tumor heterogeneity and personalized cancer medicine: are we being outnumbered? Future Oncol 2014;10:417-28.
7. Reddig A, Roggenbuck D, Reinhold D. Comparison of different immunoassays for gammaH2AX quantification. J Lab Precis Med 2018;3:80.
8. Ruhe M, Rabe D, Jurischka C, et al. Molecular biomarkers of DNA damage in diffuse large-cell lymphoma—a review. J Lab

Precis Med 2019;4:5.
9. Sarkozy C, Coiffier B. Diffuse large B-cell lymphoma in the elderly: a review of potential difficulties. Clin Cancer Res 2013;19:1660-9.
10. Sowa M, Reddig A, Schierack P, et al. Phosphorylated histone 2AX foci determination in capillary blood mononuclear cells. J Lab Precis Med 2018;3:45.
11. Lengert N, Mirsch J, Weimer RN, et al. AutoFoci, an automated high-throughput foci detection approach for analyzing low-dose DNA double-strand break repair. Sci Rep 2018;8:17282.
12. Rothkamm K, Horn S. gamma-H2AX as protein biomarker for radiation exposure. Ann Ist Super Sanita 2009;45:265-71.
13. Moquet J, Barnard S, Staynova A, et al. The second gamma-H2AX assay inter-comparison exercise carried out in the framework of the European biodosimetry network (RENEB). Int J Radiat Biol 2017;93:58-64.
14. Schneider J, Weiss R, Ruhe M, et al. Open source bioimiage informatics tools for the analysis of DNA damage and associated biomarkers. J Lab Precis Med 2019. [Epub ahead of print].
15. Lippi G, Tarperi C, Danese E, et al. Middle-distance running and DNA damage in diabetics. J Lab Precis Med 2018;3:18.
16. Lippi G, Buonocore R, Tarperi C, et al. DNA injury is acutely enhanced in response to increasing bulks of aerobic physical exercise. Clin Chim Acta 2016;460:146-51.
17. Korkmaz KS, Butuner BD, Roggenbuck D. Detection of 8-OHdG as a diagnostic biomarker. J Lab Precis Med 2018;3:95.
18. Bouwman P, Jonkers J. The effects of deregulated DNA damage signalling on cancer chemotherapy response and resistance. Nat Rev Cancer 2012;12:587-98.
19. Kryston TB, Georgiev AB, Pissis P, et al. Role of oxidative stress and DNA damage in human carcinogenesis. Mutat Res 2011;711:193-201.
20. Cadet J, Ravanat JL, TavernaPorro M, et al. Oxidatively generated complex DNA damage: tandem and clustered lesions. Cancer Lett 2012;327:5-15.
21. Debelec-Butuner B, Bostanci A, Heiserich L, et al. Automated Cell-Based Quantitation of 8-OHdG Damage. Methods Mol Biol 2016;1516:299-308.
22. Rödiger S, Liefold M, Ruhe M, et al. Quantification of DNA double-strand breaks in peripheral blood mononuclear cells from healthy donors exposed to bendamustine by an automated γH2AX assay—an exploratory study. J Lab Precis Med 2018;3:47.

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