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The role of DNA damage in diabetic complications

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Mechanistic and clinical data indicate that DNA damage contributes to the pathogenesis and progression of diabetic complications. Thus, DNA damage and its signalling are entering the field of diabetology.

Blood levels of glucose, oral glucose load, HbA_{1c} and insulin sensitivity predict the development of diabetic complications but have low sensitivity[1]. In addition, none of the currently available treatments result in remission of existing diabetic complications. Thus, something in addition to elevated levels of glucose must drive diabetic complications.

Association between metabolism, DNA damage and repair

Metabolism generates reactive metabolites (such as dicarbonyls and reactive oxygen and nitrogen species) through several interconnected pathways (Supplementary Box 1). Excess generation and decreased detoxification (by enzymes such as glyoxalase 1, glyoxalase 2, aldo-keto reductases or dehydrogenases) results in the accumulation of genotoxic reactive metabolites[2]. Their action leads to various types of DNA damage, such as DNA double-strand breaks, DNA interstrand crosslinks, DNA single-strand breaks and replication stress (Fig. 1 and Supplementary Table 1). Studies using mouse models and clinical data show that DNA double-strand breaks are common in diabetes mellitus, and often occur together with DNA interstrand crosslinks and replication stress[1,3,4]. The persistent presence of DNA double-strand break markers in preclinical models and in patients with diabetes mellitus indicates a compromised DNA repair system[1].

One of the many reasons for impaired DNA repair in diabetes mellitus is the hyperglycaemia-induced perturbed NAD^+–NADH equilibrium[3]. This perturbation reduces the availability of free PARP1 for the non-homologous end-joining repair pathway, which accounts for more than 80% of the repair in differentiated tissues[3]. In addition, the activity of DNA methyltransferase 1 (an enzyme that repairs DNA double-strand breaks) is decreased in mouse models and in human cell-based models of diabetes mellitus, which contributes to a change in epigenetic signature[5]. Furthermore, increased histone acetylation, such as at lysine 9 of histone H3 (H3K9ac), restricts chromatin accessibility and has been linked to compromised DNA repair[5].

Dicarbonyls and reactive oxygen species generated in diabetes mellitus also interfere with DNA integrity by affecting the accurate progression of the replication fork[4]. As a result, there is an increased frequency of chromosome separation from kinetochores at the anaphase plate, which causes an uneven distribution of chromosomes and an increased frequency of micronuclei. This effect is common in patients with diabetic nephropathy[4]. Rupturing of the micronuclear membrane leads to activation of the cytosolic DNA sensing programme, marked by the type I IFN signalling cascade[4].

The shift in the intracellular localization of mitochondrial enzymes (hexokinase 2, fumarase and ATP citrate lyase) also contributes to the impairment of DNA repair that is associated with diabetes mellitus by affecting the availability of energy currency (ATP) and reducing potentials (NAD^+–NADH)[6]. This finding points to the pivotal role of mitochondrial dysfunction coupled to impaired DNA repair in the development and progression of diabetic complications.

From DNA damage to cell dysfunction

The build-up of DNA damage results in the activation of the persistent DNA damage signalling (PDDS) cascade (Fig. 1). The activation of this cascade directs cells to senescence, which is characterized by the secretion of various inflammatory cytokines in what is commonly termed the senescence-associated secretory phenotype (SASP)[3]. The inflammatory, insulin-resistant and profibrotic microenvironment is central to the fibrosis associated with organ failure in diabetes mellitus. Experimental proof for this concept comes from mouse studies that show the resolution of senescence, the SASP and fibrosis after reconstitution of DNA repair[3]. Clinical observations show that patients with type 1 diabetes mellitus (T1DM) and an intact DNA repair system rarely develop organ complications[1,7]. This DNA damage-driven cascade explains how DNA damage might predispose towards microvascular and macrovascular disease and neurodegeneration, which finally affects organ function in patients with diabetes mellitus[1,8]. The signalling cascade triggered by DNA damage is further fuelled by the Western lifestyle, smoking, ageing and socioeconomic and psychological factors (Supplementary Box 2), which expedite the ongoing pathological cascade.

The two-hit or multiple-hit hypothesis

Markers of DNA damage signalling, senescence and the SASP can discriminate between patients with and without progression of organ complications associated with diabetes mellitus[1,7]. These data point to a two-hit or multiple-hit explanation for diabetic complications (Fig. 1). The first hit comes from endogenous genotoxins generated by the metabolism of glucose, lipids or other energy carriers (Supplementary Box 1). Accumulated DNA damage triggers PDDS, which results in senescence, and the SASP-associated release of cytokines and growth factors serves as a second hit. The PDDS-associated cascade can be affected by lifestyle-associated auxiliary factors (Supplementary Box 2), which represent a potential third hit. Genetic predisposition is one of the factors that explain why some patients are more, and others are less, prone to develop complications[5]. Future work should explore whether these markers help to identify patients who are most likely to benefit from a DNA-protecting or senolytic therapy.

The therapeutic options

Detoxifying reactive aldehydes, dicarbonyls and reactive oxygen species has an insulin-sensitizing and organ-protective effect[2,9] (level 1 in Fig. 1). This finding suggests that an intervention that targets DNA

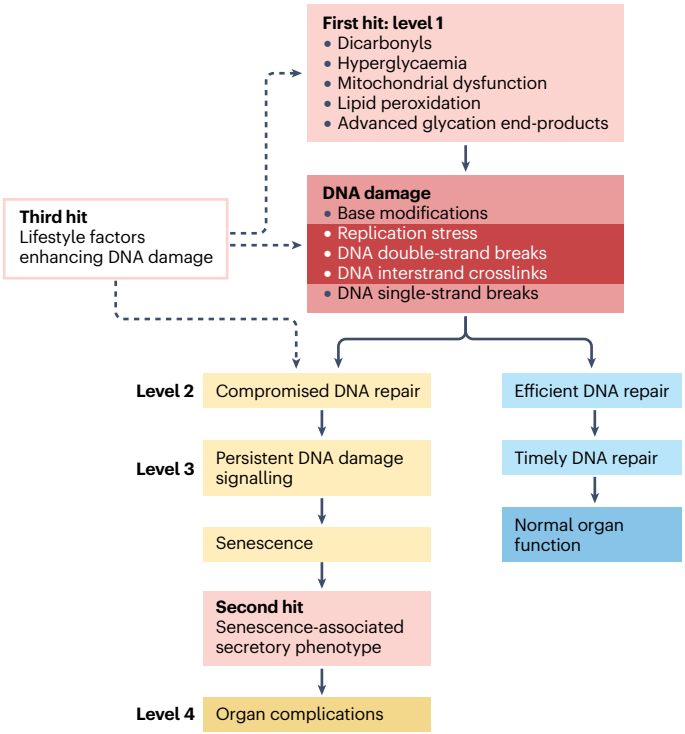

Fig. 1 | Causes and types of DNA damage in individuals with diabetes mellitus. Signalling associated with DNA damage or repair might affect the onset and progression of organ complications of diabetes mellitus.

repair might prevent diabetic complications. However, whether treatment at this level can result in remission of existing complications remains unknown. Reconstitution of a hyperactive form of nuclear RAGE (level 2 in Fig. 1) can improve DNA repair and suppress PDDS, senescence and the SASP in mouse models of T1DM and type 2 diabetes mellitus (T2DM)[1,3,7,10]. Thus, intervention at the level of DNA repair is able not only to stop the PDDS-driven cascade but also to cause remission of existing complications. Senescence has an important role in developing microvascular and macrovascular disease (level 3 in Fig. 1). Activated protein C reduces the incidence of senescence and, thereby, the severity of diabetic nephropathy[1,8]. Thus, senolytic therapies might block the downstream pathological effects of senescence. Inhibition of cytokines and growth factors might also ameliorate diabetic complications (level 4 in Fig. 1). However, it remains unknown whether their effect on the development or the progression of complications is similar to inhibition at the levels upstream of the SASP. Studies that are investigating the DNA-protecting, senescence-reducing, anti-inflammatory and SASP-inhibiting effects of drugs already in clinical use in diabetology provide indirect support for the role of PDDS in the development and progression of diabetic complications (Supplementary Table 2).

Open questions

Many questions remain open. For instance, the PDDS-specific differences between T1DM and T2DM — and how novel therapeutics could address these differences — are unclear. Answering this question will help to precisely target new therapies for T1DM and T2DM and individual risk factor profiles. How organ specificity could be explained is also unknown. Markers for the PDDS cascade show no correlation to retinopathy and a weak correlation to the progression of metabolic dysfunction-associated steatotic liver disease in T2DM, but are prominent in diabetic lung and kidney disease. Whether all kinds of DNA damage (DNA double-strand breaks, DNA interstrand crosslinks and replication stress) co-occur, or whether they are specific to particular organs, cells, risk factors or people, is unclear. Addressing this question will help to tailor future therapies specifically directed at DNA repair. The most effective level at which targeting the PDDS- associated cascade is a potential treatment, and whether we can delay the point of no return and achieve remission in all instances, is not known. Answering this question is important for the development of targeted therapies for diabetic complications.

Conclusion

The knowledge of the contribution of a DNA damage-driven cascade to the pathogenesis of diabetic complications and the experimental data on reversal of complications after reconstitution of DNA repair have several implications. These advances help to define new subgroups of patients with diabetes mellitus and help to develop new therapeutic options, targeting the DNA damage-driven levels of the cascade described. Thus, it is likely that the field of DNA repair will soon enter clinical diabetology.

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Competing interests

The authors declare no competing interests.

Additional information

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