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Aldehyde dehydrogenase 2 in aplastic anemia, Fanconi anemia and hematopoietic stem cells

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ABSTRACT

Maintenance of the hematopoietic stem cell (HSC) compartment depends on the ability to metabolize exogenously and endogenously generated toxins, and to repair cellular damage caused by such toxins. Reactive aldehydes have been demonstrated to cause specific genotoxic injury, namely DNA interstrand cross-links. Aldehyde dehydrogenase 2 (ALDH2) is a member of a 19 isoenzyme ALDH family with different substrate specificities, subcellular localization, and patterns of expression. ALDH2 is localized in mitochondria and is essential for the metabolism of acetaldehyde, thereby placing it directly downstream of ethanol metabolism. Deficiency in ALDH2 expression and function are caused by a single nucleotide substitution and resulting amino acid change, called *ALDH2*2*. This genetic polymorphism affects 35–45% of East Asians (about ~560 million people), and causes the well-known Asian flushing syndrome, which results in disulfiram-like reactions after ethanol consumption. Recently, the *ALDH2*2* genotype has been found to be associated with marrow failure, with both an increased risk of sporadic aplastic anemia and more rapid progression of Fanconi anemia. This review discusses the unexpected interrelationship between aldehydes, ALDH2 and hematopoietic stem cell biology, and in particular its relationship to Fanconi anemia.

Contents

1. Introduction

A central problem in hematology is the limited lifespan of mature non-lymphoid cells, which necessitates constant production of new

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blood cells. In humans, the estimated lifespan of circulating red blood cells (RBCs) is 120 days, polymorphonuclear neutrophils (PMNs) 2 days, and platelets 5–10 days. To maintain the blood system, approximately 2×10^{11} RBCs, 1.6×10^{11} PMNs, and 10^{11} platelets are produced daily [1–4]. The evolutionary resolution of this problem in mammals is based on a hierarchy of self-renewing multipotent hematopoietic stem cells (HSC), which give rise to non-self-renewing, lineage committed hematopoietic progenitor cells (HPC) capable of massive expansion and differentiation into mature blood cells.

The dependence of blood cell production on a limited number of HSC and HPC (hereafter collectively referred to as HSPC) means that protection from potential toxins is essential for maintenance of the hematologic system (see Fig. 1). For example, the generation of blood cells within the intramedullary marrow space of heavily calcified bones probably protects cells from typical doses of external ionizing radiation. Immature HSPC express a number of proteins which appear to protect them from toxicological injury. For example, the ABC transporter protein MDR1 expressed by HSC increases the export of various xenobiotics, including some chemotherapy drugs [5].

Because genotoxic injury is inevitable, an important protective mechanism is the expression of various proteins involved in DNA repair pathways [6]. These pathways include those for repair of single strand breaks, such as base excision repair (BER), nucleotide excision repair (NER), and mismatch repair (MMR). To repair double strand breaks, cells express pathways for non-homologous end joining (NHEJ), homologous recombination (HR), or microhomology-mediated end joining (MMEJ). Additionally, cells can use tolerance methods to continue to replicate DNA around lesions, called translesion synthesis (TLS).

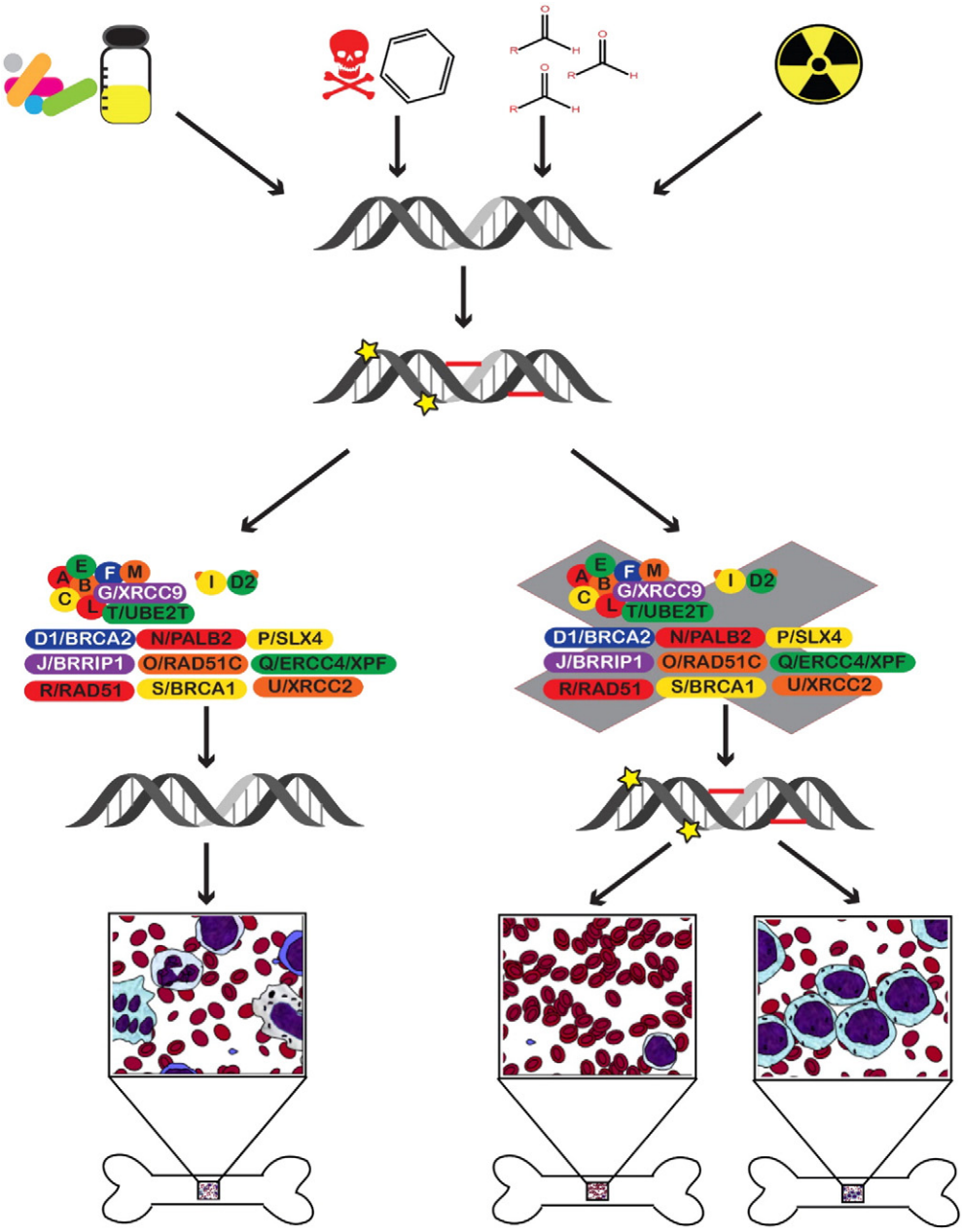

Fig. 1. Genomic instability and bone marrow failure: the genome is subject to a variety of different insults, including chemotherapy drugs, benzene and other toxic substances, radiation, and aldehydes (RCH = O). These can induce different types of DNA damage, including adduct formation, single and double strand breaks, and interstrand crosslinks. When the damage is appropriately repaired by DNA repair pathways, one of which is the FA pathway (depicted), there is no damage to HSPC in the bone marrow (depicted by a normal mixture of cells in the left inset). When the damage is not adequately repaired by DNA repair pathways, or by the FA pathway specifically, loss of HSPC can occur, leading to bone marrow failure (aplastic anemia, shown in the middle inset), or acute myelogenous leukemia (AML) shown on the right.