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Research review paper

Natural compounds and pharmaceuticals reprogram leukemia cell differentiation pathways

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ABSTRACT

In addition to apoptosis resistance and cell proliferation capacities, the undifferentiated state also characterizes most cancer cells, especially leukemia cells. Cell differentiation is a multifaceted process that depends on complex regulatory networks that involve transcriptional, post-transcriptional and epigenetic regulation of gene expression. The time- and spatially-dependent expression of lineage-specific genes and genes that control cell growth and cell death is implicated in the process of maturation. The induction of cancer cell differentiation is considered an alternative approach to elicit cell death and proliferation arrest. Differentiation therapy has mainly been developed to treat acute myeloid leukemia, notably with all-trans retinoic acid (ATRA). Numerous molecules from diverse natural or synthetic origins are effective alone or in association with ATRA in both in vitro and in vivo experiments. During the last two decades, pharmaceuticals and natural compounds with various chemical structures, including alkaloids, flavonoids and polyphenols, were identified as potential differentiating agents of hematopoietic pathways and osteogenesis.

Contents

Abbreviations: ABL, Abelson; ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BC, blast crisis; BCR, breakpoint cluster region; BMP, bone morphogenetic protein; CBP, CREB-binding protein; CDK, cyclin dependent kinase; CEBPα, CCAAT/enhancer binding protein α; CFU-E, colony forming units-erythroid; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; EpoR, erythropoietin receptor; ETO, eight twenty-one; ETS, E26 transformation-specific; 5-FU, 5-fluorouracil; FDA, food and drug administration; FGF, fibroblast growth factor; FLT3, FMS-like tyrosine kinase 3; FOG-1, friend of GATA-1; GABA, gamma amino butyric acid; GABPα, GA binding protein alpha; GP, glycoprotein; GPA, glycophorin A; GTP, guanosine triphosphate; HDAC, histone deacetylase; Hh, hedgehog; hMSC, human mesenchymal stem cell; HSC, hematopoietic stem cells; HSP, heat-shock protein; IFN, interferon; IL, interleukin; IRF-1, interferon regulatory factor; JAK, Janus kinase; LDB1, Lim domain-binding protein; LMO2, Lim-only protein 2; lncRNA, long non-coding RNA; MAPK, mitogen-activated protein kinase; miR, microRNA; MM, multiple myeloma; NBT, nitro-blue tetrazolium chloride; NF-E2, nuclear factor-erythroid 2; NuRD, nucleosome remodeling and deacetylase; PBGD, porphobilinogen deaminase; PI3K, phosphoinositide 3 kinase; PKC, protein kinase C; PLSCR1, phospholipid scramblase 1; PML–RARα, promyelocytic leukemia/retinoic acid receptor α; PPIase, peptidyl-prolyl cis-trans isomerase; PRMT1, protein arginine N-methyltransferase 1; RANKL, receptor activator of NF-κB ligand; RBP, RNA-binding protein; RUNX, runt-related transcription factor; RXR, retinoid-X-receptor; STAT, signal transducer and activator of transcription; Tal-1, T-cell acute lymphocytic leukemia protein 1; TGFβ, transforming growth factor beta; TNFα, tumor necrosis factor α; TPA, 12-O-tetradecanoylphorbol-13-acetate; VD3, 1,25-dihydroxyvitamin D3; VDR, vitamin D3 receptor; VPA, valproic acid; WHO, World Health Organization.

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1. Introduction

Acquiring a specific cell function likely constitutes one of the most complex biological processes. Cell differentiation requires the accurate and coordinated regulation of the expression of many genes at the spatial and temporal levels. In addition to the control of the expression of specific genes, the management of cell proliferation and survival is crucial to generate functional cells. All biomolecules that exist in a cell are involved in differentiation processes, including transcription and chromatin remodeling factors, as well as non-coding RNAs such as micro(mi)RNAs and long non-coding (lnc)RNAs, which interact in a very complex regulatory network that manages gene expression. Together, the effectors of cell regulation interact and lead to the ultimate stage of differentiation in a stepwise manner.

1.1. Differentiation therapy

In addition to the deregulation of cell proliferation and survival, the consecutive absence of normal differentiation characterizes most malignant cells. Therefore, the molecular mechanisms involved in the differentiation process have been considered a potential therapeutic target in tumor cells. Pre-clinical models were developed as early as the 1980s (Reiss et al., 1986), and the concept of concomitantly inducing cancer cell differentiation and cell proliferation arrest has become an alternative to cytotoxic chemotherapies. The aim was to modulate signaling pathways and the expression of specific genes to lead cancer cells towards a more advanced stage of differentiation and invert the growth/differentiation plot. Rather than killing cells via the activities of cytotoxic and unselective drugs, this therapy aimed to reprogram malignant and useless cells into functional ones using subtoxic doses of differentiating agents. The induction of tumor cell differentiation has been shown to be effective in the in vitro and in vivo treatments of several types of cancer cells (Leszczyniecka et al., 2001), and differentiation-inducing therapy was recently proposed to treat malignant gliomas (Liu et al., 2010). A variety of compounds that can induce cancer cell differentiation have been reported for three decades. Compounds with various molecular structures, including retinoic acid (Breitman et al., 1980; Castaigne et al., 1990), butyrate derivatives (Newmark et al., 1994), dimethyl sulfoxide (Breitman, Selonick, 1980), and anthracyclines (Morceau et al., 1996a; Sato et al., 1992; Trentesaux et al., 1993), displayed differentiation activities in vitro in leukemia cells via diverse mechanisms of action. The primary effective compounds, described as differentiation-inducing agents, were vitamin D derivatives, retinoid, interferon and polar-planar compounds. Most of these molecules were particularly active on myeloid leukemia cells, which differentiated into morphologically and functionally mature cells (Paquette and Koeffler, 1992).

Leukemia is a cancer that affects the blood, bone marrow and lymphoid system as well as the differentiation of normal hematopoietic cells. Four main types of leukemia have been determined based on the cell lineage transformation and clinical features, namely acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL) and chronic lymphocytic leukemia (CLL). Moreover, a group of French, American and British (FAB) hematologists divided acute leukemia into subtypes; in 1976, this effort led to a classification based on the quantification of blasts, their degree of maturity and the identification of chromosomal abnormalities. Later, the World Health Organization (WHO) established a new classification based on the FAB guidelines, and this classification considered morphology as well as cytogenetic, molecular genetic, gene mutation and clinical features (Rulina et al., 2010). Molecular and cellular features in leukemia cells result from the perturbation of the normal hematopoiesis regulatory network.

1.2. Hematopoiesis regulation

Hematopoiesis is a process that leads to the continuous production and replacement of all blood cells. During embryogenesis, hematopoiesis takes place in the blood islands of the yolk sac and in the liver, spleen and lymph nodes. In adults, it occurs only in the bone marrow of sternal bones, the iliac crest and the femoral head. A small population of bone marrow cells, hematopoietic stem cells (HSC), produces hematopoietic cells in adults. HSCs are undifferentiated and multipotent cells with an increased capacity for self-renewal, proliferation and differentiation.

Most blood cells are highly differentiated with reduced protein synthesis and cell division capacity. Their lifetime varies from a few hours for neutrophils and few days for platelets to several weeks for red blood cells. Blood cells are the terminal and functional elements of the two major hematopoietic lineages, lymphoid and myeloid. The different hematopoietic cells proliferate, differentiate and complete their maturation in the bone marrow prior to entering the bloodstream and exert their function in tissues. T cells are an exception because they mature in the thymus, lymph nodes and spleen.

The regulation of the self-renewal, proliferation and differentiation of these cells involves cell–cell interactions with stromal cells from the bone marrow as well as multiple types of molecules that act in a time- and concentration-dependent manner, including cytokines, chemokines, growth factors and transcription factors (Broxmeyer et al., 1989, 2005; Wickrema and Crispino, 2007), as well as miRNAs (Mathieu and Ruohola-Baker, 2013). The following description of hematopoiesis regulation is not exhaustive because only the versatile roles of some transcription factors are shown. The deregulation of this network clearly perturbs hematopoiesis, which leads to hematological disorders, including leukemia. The GATA family of transcription factors has emerged as an essential regulator of gene expression in the different hematopoietic cell types. Three of the six members, GATA-1, GATA-2 and GATA-3, are expressed and functional in hematopoietic cells, whereas GATA-4, GATA-5 and GATA-6 are expressed in different tissues derived from the mesoderm and endoderm, such as the heart, liver, lung, gonads, and intestine (Molkentin, 2000). GATA-1 plays a crucial role in the suitable development of erythroid cells, especially during the later stages (Pevny et al., 1995), as well as during the differentiation of megakaryocytes, eosinophils and mast cells (Harigae et al., 1998; Hirasawa et al., 2002; Romeo et al., 1990). This zinc finger protein contains a N-terminal region, which confers transcriptional activity, and a C-terminal domain that allows binding to DNA and other proteins. GATA transcription factors specifically recognize the G/A/T/A sequence in the *cis*-regulatory regions of genes. GATA-binding sites are largely represented in most erythroid-related promoter/enhancer genes, including globins, heme metabolism enzymes, glycophorine A (GPA) and erythropoietin receptor (EpoR), as well as in the anti-apoptotic Bcl-xL gene (Gregory et al., 1999). Moreover, GATA-binding sites are present in the promoters of genes that are specifically involved in megakaryocyte differentiation, such as CD42a/glycoprotein (GP)9, GP2b and the thrombopoietin receptor CD110/c-Mpl (Szalai et al., 2006). GATA-1 can interact with other nuclear proteins via its C-terminal domain, resulting in the activation or repression of target gene expression in erythroid (Song et al., 2004) and megakaryocytic (Elagib et al., 2003) differentiation. The interaction of GATA-1 with its cofactor “Friend of GATA” (FOG)-1 is essential for the success of erythropoiesis and megakaryopoiesis (Dore and Crispino, 2011; Tsang et al., 1997). Other studies have shown that a factor involved in chromatin remodeling, NuRD, interacts with the N-terminus of FOG-1 and that this interaction is important for the activation or repression of genes regulated by the GATA-1/FOG-1 complex (Miccio et al., 2010; Vicente et al., 2012). The interaction between GATA-1 and NuRD/FOG-1 is required for the proper development of megakaryocytes. In addition to FOG-1, many proteins interact and form complexes around GATA-1 to modulate its transcriptional activity. LMO2 (Lim-only protein 2) is a “zinc finger”

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