frequencies from 16% to 28%. The MDS clinical trial of List et al. (202) demonstrated that lenalidomide is specifically toxic to cells containing a specific deletion in chromosome 5, namely, the 5q31 deletion. The inclusion criteria expressly required the 5q31 deletion in the affected cells of the study subjects. Therapy with lenalidomide resulted in remission in about half of the patients. The drug also restored production of red blood cells, apparently by its effect in suppressing the clone of myelodysplastic cells containing the 5q31 deletion. The investigators found that, "lenalidomide is selectively cytotoxic to 5q-deletion clones and restores red cell production in part by suppressing the myelodysplastic clone" (203).

g. Mechanism of Action of Lenalidomide

Studies of the mechanism of action of lenalidomide by Verhelle et al. (204) and Escoubet-Lozach et al. (205) revealed that the drug stimulates an increase in expression of the *p21WAF-1* gene, with the consequent halt in proliferation. In detail, $p21^{WAF-1}$, at increased levels, combines with various kinases, inhibits the kinases, where the result is reduced phosphorylation of pRB, and a consequent block of the cell cycle. In contrast, when lenalidomide is added to normal cells (not cancer cells) the drug does not halt proliferation of the cells.

h. Mechanism of Action of 5-Aza-Deoxycytidine

5-Aza-deoxycytidine is a hypomethylating agent, that is, it reduces the amount of methyl groups that are naturally attached to deoxycytidine residues of the chromosomal DNA. As a consequence of this reduced methylation, genes are activated in the target cells, where the activation of genes that cause cell differentiation causes a cancerous cell to be noncancerous. The mechanism of action of 5-aza-deoxycytidine likely includes the following scenario (206). The drug is an analog of deoxycytidine, and is incorporated into the chromosome during DNA replication. Normally, specific residues of deoxycytidine in the mammalian chromosome are enzymatically methylated. Methylation is catalyzed by DNA methyltransferase. But when this enzyme attempts to catalyze the methylation of 5-aza-deoxycytidine, the enzyme becomes covalently bound to the DNA and is trapped. The consequence is a reduction of the amount of this enzyme in the cell, failure to methylate DNA, and the generation of under-methylated chromosomes.

[202]List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. New Engl. J. Med. 2006;355:1456–65.

[203]List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. New Engl. J. Med. 2006;355:1456–65.

[204]Verhelle D, Corral LG, Wong K, et al. Lenalidomide and CC-4047 inhibit the proliferation of malignant B cells while expanding normal CD34 + progenitor cells. Cancer Res. 2007;67:746–55.

[205]Escoubet-Lozach L, Lin IL, Jensen-Pergakes K, et al. Pomalidomide and lenalidomide induce p21 WAF-1 expression in both lymphoma and multiple myeloma through a LSD1-mediated epigenetic mechanism. Cancer Res. 2009;69:7347–56.

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