① Line 7 : MYC is a transcription factor that ~~reduces~~ proliferation ✗

↳ it should be induces or increases

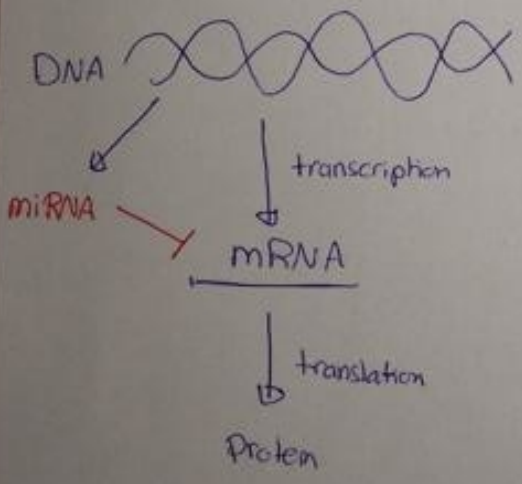
② Examples on the role of miRNA in carcinogenesis:-

a) downregulation of miRNAs in some Leukemias and lymphomas results in increased expression of BCL-2, which is an anti-apoptotic gene.

b) downregulation of miRNAs causes upregulation (over-expression) of the RAS and MYC oncogenes which has been detected in lung tumors and in certain B-cell leukemias, respectively.

↑RAS → Lung tumors
↑MYC → B-cell leukemia

To Summarize :-



- miRNA acts as a negative regulator for genes expression either by blocking translation or degrading the mRNA.

↑ miRNA → ↓ oncogene ⇒ no Cancer

↓ miRNA , ↑ oncogene ⇒ Cancer

↑ miRNA , ↓ TSG ⇒ Cancer

↓ miRNA , ↑ TSG ⇒ no Cancer

TSG ≡ Tumor Suppressor Gene.

Page 11 :-

. DNA methylation (Line 8 → Line 19)

Example on cancer epigenetics :-

CDKN2A (Cyclin Dependent Kinase Inhibitor 2A) is a complex locus that encodes two tumor suppressors ; P14/ARF and P16/INK4a which are produced from 2 different reading frames.

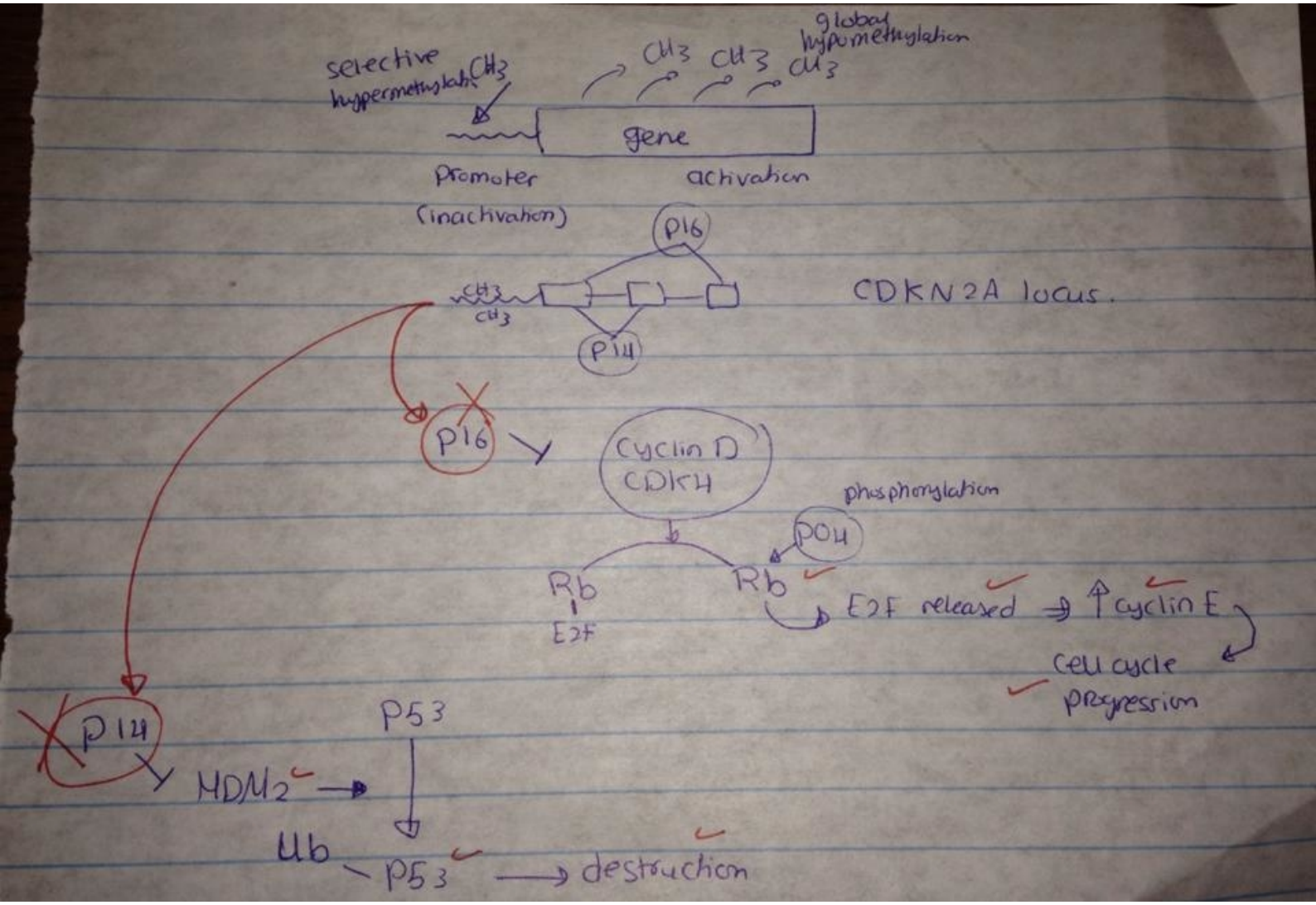
- To understand the mechanism :-

[1] P16 inhibits cyclin D and CDK4, thus preventing them from phosphorylating Rb (Rehnoblastoma) ⇒ E_2F won't be released ⇒ cyclin E won't be activated ⇒ no cell cycle progression

Due to epigenetics in CDKN2A locus, there will be a global hypomethylation of this locus + selective (specific) hypermethylation of its promoter (Tumor Suppressor Gene). As a result, P16 won't be produced ⇒ no inhibition of cyclin D & CDK4 ⇒ Rb will be phosphorylated ⇒ E_2F is released, it will activate cyclin E ⇒ cell cycle progression ⇒ activation without control will occur.

[2] P14 inhibits MDM_2 [ubiquitin ligase], so $P53$ won't be ubiquitylated ⇒ $P53$ is active and able to sense DNA damage

• If P14 isn't produced (due to epigenetics), MDM2 won't be inhibited and it'll ubiquitylate $P53$ ⇒ $P53$ will be destroyed by the proteosomal-ubiquitin pathway, so $P53$ won't be there to sense DNA damage neither stop G1 − S transition.


selective hypermethylation
CH3
CH3 CH3 CH3
global hypomethylation
gene
promoter (inactivation)
activation
P16
P14
CDKN2A locus.
P16
cyclin D
CDK4
phosphorylation
PO4
Rb
E2F
Rb
E2F released
cyclin E
cell cycle progression
P14
MDM2
P53
Ub
P53
destruction