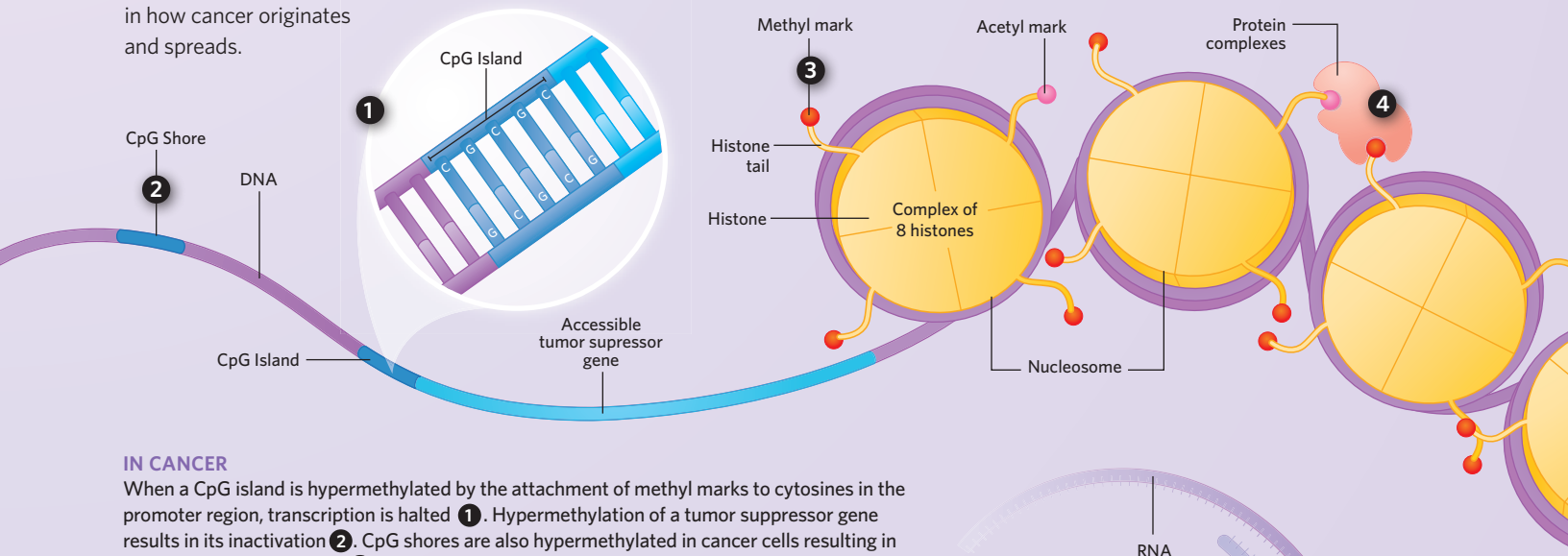
CANCER AND THE EPIGENOME

In cancer cells the epigenetic landscape is highly altered. Hypermethylation of certain stretches of DNA is the most well-studied epigenetic modification in cancer, and each tumor type has its own specific pattern. Histone modifications also occur, as does remodeling of chromatin. And disruption of noncoding RNA sequences, the so-called "dark genome," that code for microRNAs also seems to play a role in how cancer originates and spreads.

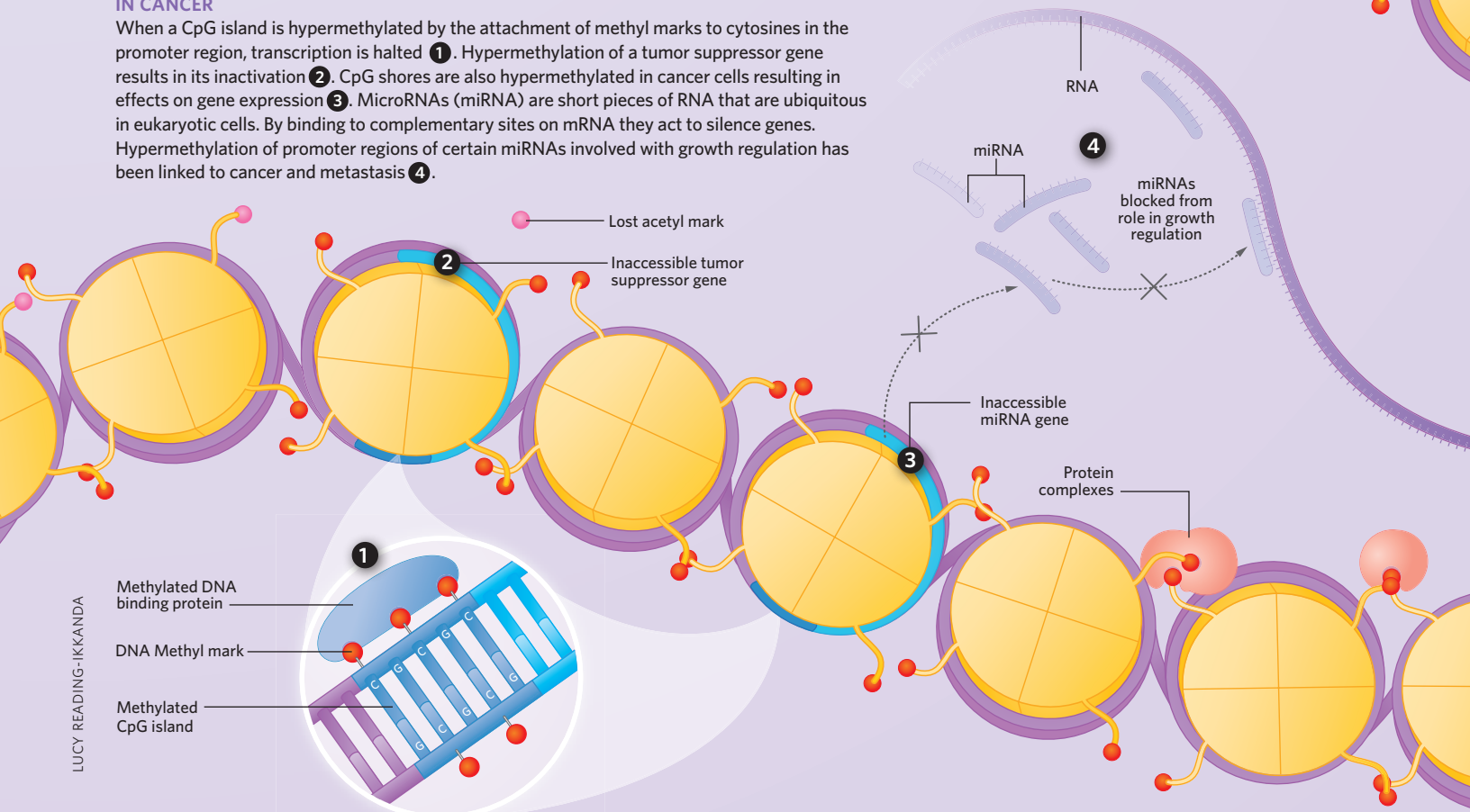
EPIGENETIC MARKS IN NORMAL CELLS

A CpG island consists of a stretch of some 300 to 3,000 DNA bases where clusters of cytosine and guanine dinucleotides make up about half the sequence ❶. More than 60% of these islands are associated with the promoter regions of genes and are not methylated in genes that are actively transcribed. Located some 2 kb from these promoter regions are stretches of DNA that are not quite so rich in CpG, known as CpG shores ❷. Methylation of these cytosines results in gene inactivation and is associated with structural changes in chromatin that occur during differentiation and chromosome imprinting in developing embryos. Inactive chromatin consists of DNA tightly wrapped around a core of eight histones whose projecting tails are modified with various covalent marks ❸. Protein complexes associate with chromatin and control gene activation or repression by adding or removing marks such as methyl and acetyl groups to histones or methyl groups to cytosine bases in the DNA chain ❹.



IN CANCER

When a CpG island is hypermethylated by the attachment of methyl marks to cytosines in the promoter region, transcription is halted ❶. Hypermethylation of a tumor suppressor gene results in its inactivation ❷. CpG shores are also hypermethylated in cancer cells resulting in effects on gene expression ❸. MicroRNAs (miRNA) are short pieces of RNA that are ubiquitous in eukaryotic cells. By binding to complementary sites on mRNA they act to silence genes. Hypermethylation of promoter regions of certain miRNAs involved with growth regulation has been linked to cancer and metastasis ❹.



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