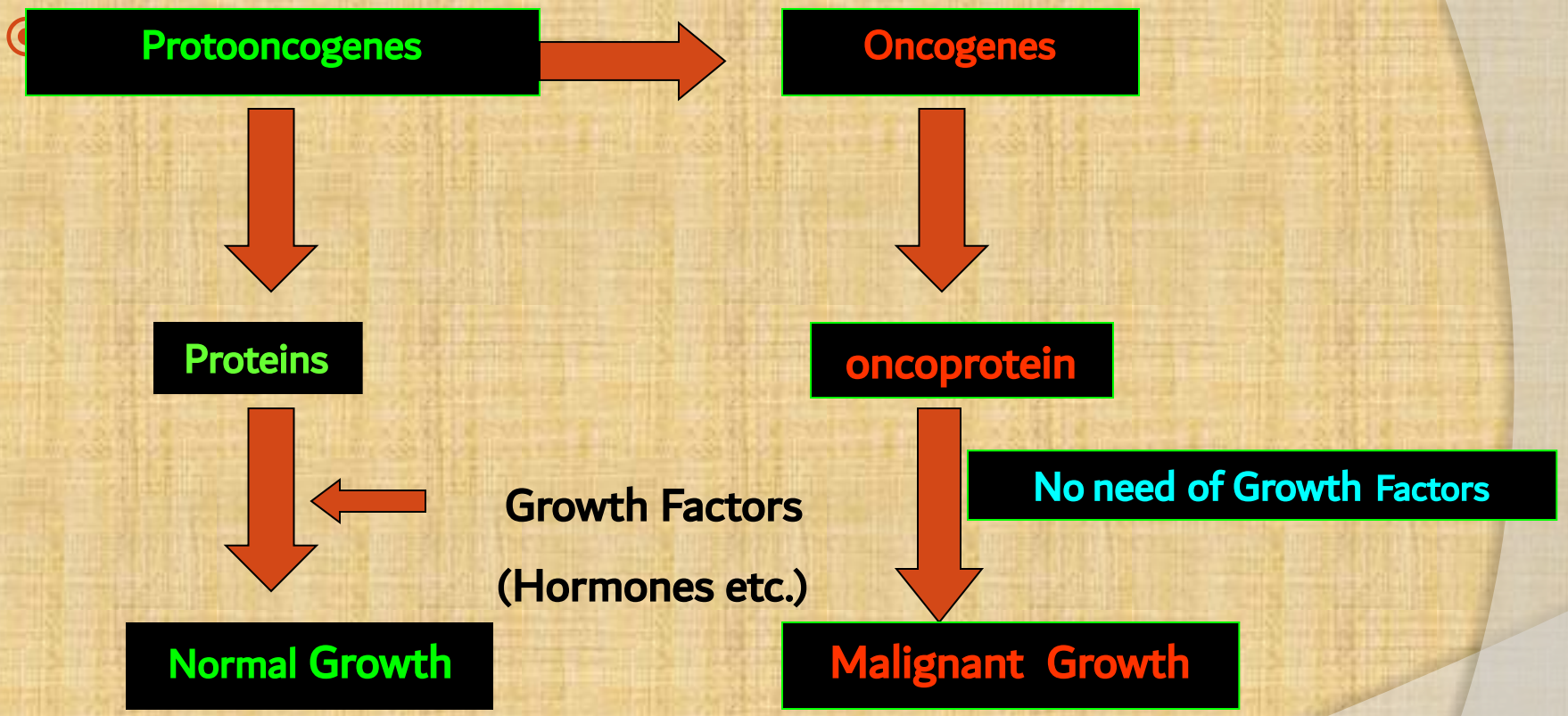
Protooncogenes and oncogenes



Oncoprotein similar functions as their normal counterparts (proto-oncogenes) but make cells *self-sufficient to grow*

ONCOGENES ENCODE

- Transcription Factors
- Growth regulating proteins
- Proteins involved in cell survival
- Cell-Cell interactions
- Cell-Matrix interactions
  - Oncogenes are **Domanant** b/c mutation of a single allele can lead to cellular transformations

Tumor Suppressor Genes

- Prevent uncontrolled growth
- Usually **both** alleles must be damaged but occasionally a single allele can promote transformation- Haploinsufficiency
- Two types-Governors(RB) & Guardians(TP53)
- **Governors** remove brakes on cell proliferation
- **Guardians** sense genomic damage

- **Genes involved in apoptosis and DNA repair** may act like:
  - proto-oncogenes (Loss of one copy is sufficient)
  - or tumor suppressor genes (Loss of both copies)

GENETIC LESIONS IN CANCER

- **May be subtle e.g;**
  - Point mutations
  - Insertions
  - Deletions
- **Or may be large enough to produce:**
  - Karyotypic changes

KARYOTYPIC CHANGES IN TUMORS

- Balanced Translocations
  1. Overexpression of protooncogenes-Burkitt lymphoma-t 8;14
  2. Creat fusion genes- Philadelphia ch in CML
- Deletions
  - Deletions involving 13q14-the sit of RB gene are asso with Retinoblastoma and deletion of 17p is asso with p53
- Gene Amplifications
  - Produce several 100 copies of protooncogenes
  - NMYC in Neuroblastoma & ERBB2(HER2/NEU)in Breast cancer

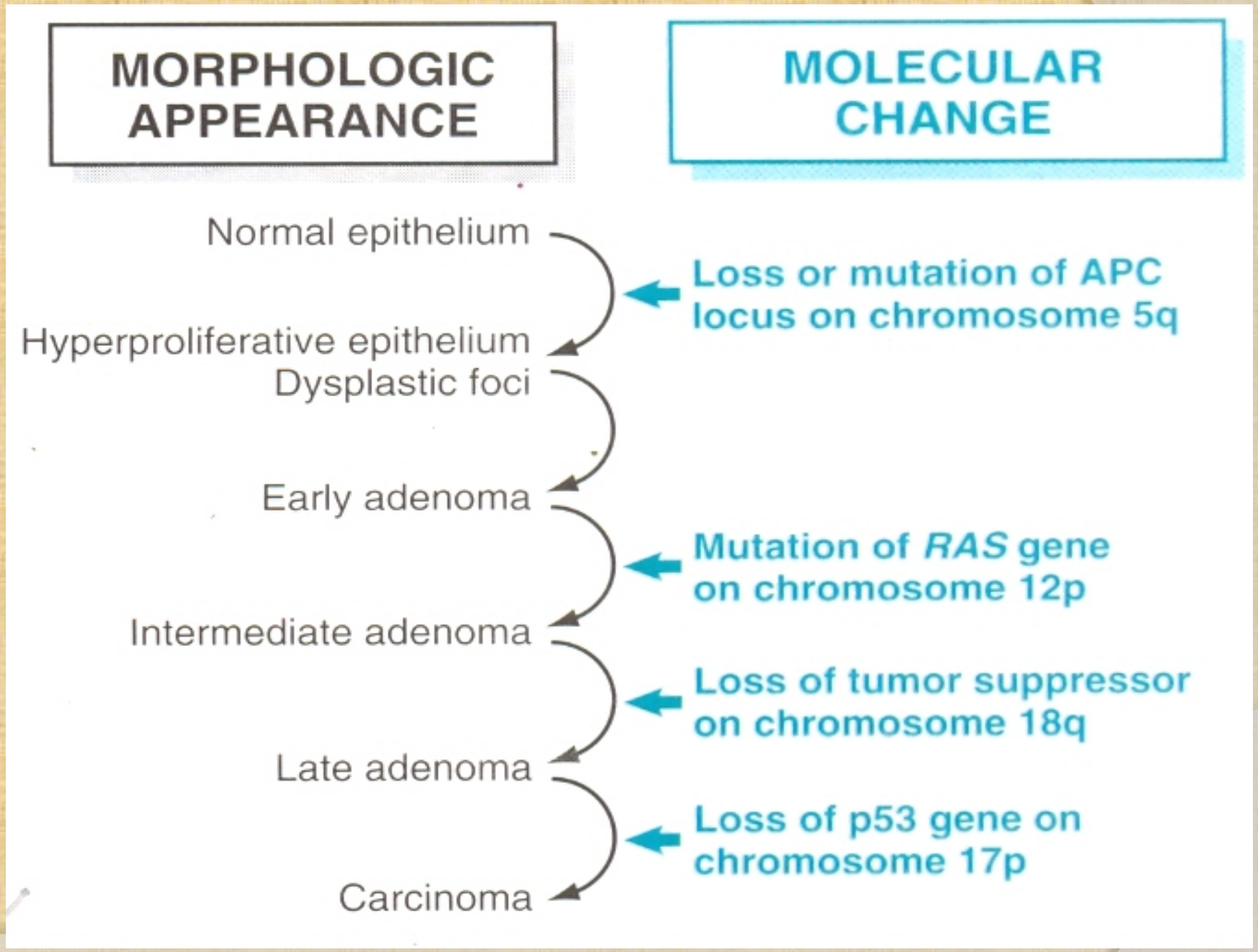
MicroRNAs & Cancer

- Are noncoding, single stranded RNAs, 22 nucleotides in length, function as –ve regulator of genes
- Participate in neoplastic transformation either by increasing expression of oncogenes or reducing the expression of tumor suppressor genes
- If miRNA inhibits translation of an oncogene, a reduction in quantity or function of that miRNA will lead to overexpression of oncogene product.
- Conversely if target of miRNA is a TSGene then overactivity of miRNA can reduce TS protein

Epigenetic Modifications & Cancer

- Reversible heritable changes in gene expression that occur without mutation but by methylation of promoter
- In normal cells,major portion of genome is not expressed
- These regions of genome are silenced by DNA methylation & histone modifications
- But cancer cells are characterized by a global DNA hypomethylation & selective promoter localized hypermethylation

- **Carcinogenesis: A multiple-step process**
  - Results from accumulation of multiple genetic alterations that collectively give rise to transformed phenotype


MORPHOLOGIC APPEARANCE
MOLECULAR CHANGE
Normal epithelium
Hyperproliferative epithelium
Dysplastic foci
Early adenoma
Intermediate adenoma
Late adenoma
Carcinoma
Loss or mutation of APC locus on chromosome 5q
Mutation of RAS gene on chromosome 12p
Loss of tumor suppressor on chromosome 18q
Loss of p53 gene on chromosome 17p

Hallmarks of cancer

Hallmarks of Cancer

1. Self-sufficiency in growth signals
2. Insensitivity to growth inhibitory signals
3. Evasion of apoptosis
4. Limitless replicative potential
5. Sustained angiogenesis
6. Invasion and metastasis

Self-sufficiency in growth signals