Genomic changes in tumours

Genomic changes in tumours

In normal circumstances, there is precise control of the divi - sion and proliferation of human cells. For example, various growth factors influence division by binding to specific cell surface tyrosine kinase receptors, resulting in the initiation of a complex intracellular cascade of changes . Damaged - cells may undergo apoptosis, a carefully regulated process of programmed cell death. Tumours require loss of control of cell proliferation. Abnormalities of numerous genes can a ff ect proliferation and fall into facilitate tumour development. The relevant genes two main categories, i.e. proto-oncogenes (which stimulate - cell proliferation) and tumour suppressor genes (which inhibit proliferation) but the picture is not always so straightforward. Activation of proto-oncogenes by genetic changes may induce or accelerate cell proliferation, while inhibition of tumour sup - pressor genes may remove the controls that normally prevent or retard proliferation. When a proto-oncogene contributes to cancer development, it is usually known as an oncogene. Other genetic changes can also facilitate tumorigenesis. esis. The classical model for this process is the ‘adenoma– carcinoma sequence’ of Fearon and V ogelstein, whereby the accumulation of mutations such as APC , KRAS and TP53 the colorectal mucosa corresponds broadly to the transforma tion of non-neoplastic mucosa into a colorectal adenoma and subsequently a carcinoma. Current models show that the pic ture is often very complex and di ff ers between tumours and that a simple sequence does not operate consistently . Several types of genetic abnormality can occur during tumorigenesis. The main categories of abnormalities are point mutations, fusion genes and cop y number changes. Point muta tions ar e single changes in the sequence of nucleotides in DNA and can be germline, i.e. inherited from a parent and accord ingly present in every cell in the body , or somatic, i.e. acquir at some point during life and a ff ecting only the tumour cells. Deletions and insertions (indels) of nucleotides result in a frameshift mutation. Examples include TP53 tumour suppres sor gene mutations, causing production of an abnormal p53 protein that lacks suppressor function; and mutation of the KIT gene, causing ligand-independent activation of a growth factor receptor. Fusion genes may be formed by several mechanisms, including translocations and deletions. The translocation t(14:18) in follicular lymphoma results in juxtaposition of the anti-apoptotic BCL2 to a regulatory region of an immunoglob ulin heavy chain gene, with subsequent bcl-2 overexpression. Fusion genes can result from various chromosomal changes, e.g. TMPRSS2-ERG gene fusion in prostate adenocarcinoma can occur as a result of a chromosomal deletion and causes abnormal oncogenic activation of ERG . Gene amplification refers to an increase in copy number, resulting in overexpression of the gene, and can variably result from abnormalities in DNA replica tion, chromosomal struc ture or telomeres. An example is HER2 amplification, resulting in overexpression of the growth factor in carcinomas of breast and stomach. These many types of abnormality in the genome may ultimately interfere with the function of proteins involved in regulatory processes: TP53 and KRAS

mutations are among the most common. Genetic changes can disrupt various path ways, including signal transduction (e.g. various growth factors and growth factor receptors, intracellular components such as RAS genes, APC gene), cell cycle regulators (e.g. p16 DNA repair pathways (e.g. MMR genes, BRCA1 mutations in breast carcinoma) and apoptosis (e.g. BCL2 , an inhibitor of apoptosis). DNA MMR genes play a vital role in correcting replication errors and other errors. Abnormalities of MMR genes cause instability of short tandem repeated sequences of DNA known as micr osatellites, resulting in MSI. Tumours with this char acteristic are MSI-H (high level of MSI). The relevant genes are MLH1, MSH2, MSH6 and PMS2 . MSI is a feature of around 15% of CRCs and can result either from a germline mutation in the MMR gene (Lynch syndrome) or, more often, Eric R Fearon , contemporary , Professor of Oncology , University of Michigan, Ann Arbor, MI, USA. Bert Vogelstein , b. 1949, Professor of Oncology and Pathology , Johns Hopkins Medical School, Baltimore, MD, USA. Henry Thompson Lynch , 1928–2019, Chair of Preventative Medicine, Creighton University , Omaha, NE, USA. repair gene abnormalities in tumours). in Epigenetic changes and methylation - Epigenetic factors are external to the gene sequence and can switch it on or o ff . The latter is known as epigenetic silencing - and can result from DNA methylation (addition of a methyl group to DNA), modifications of histones and RNA-associated silencing. Loss of methylation with gene activation can occur in tumours. Conversely , hypermethylation of tumour suppressor genes or of the MMR gene MLH1 can reduce or halt their - activity , favouring malignancy . - ed Genomic changes in tumours

In normal circumstances, there is precise control of the divi - sion and proliferation of human cells. For example, various growth factors influence division by binding to specific cell surface tyrosine kinase receptors, resulting in the initiation of a complex intracellular cascade of changes . Damaged - cells may undergo apoptosis, a carefully regulated process of programmed cell death. Tumours require loss of control of cell proliferation. Abnormalities of numerous genes can a ff ect proliferation and fall into facilitate tumour development. The relevant genes two main categories, i.e. proto-oncogenes (which stimulate - cell proliferation) and tumour suppressor genes (which inhibit proliferation) but the picture is not always so straightforward. Activation of proto-oncogenes by genetic changes may induce or accelerate cell proliferation, while inhibition of tumour sup - pressor genes may remove the controls that normally prevent or retard proliferation. When a proto-oncogene contributes to cancer development, it is usually known as an oncogene. Other genetic changes can also facilitate tumorigenesis. esis. The classical model for this process is the ‘adenoma– carcinoma sequence’ of Fearon and V ogelstein, whereby the accumulation of mutations such as APC , KRAS and TP53 the colorectal mucosa corresponds broadly to the transforma tion of non-neoplastic mucosa into a colorectal adenoma and subsequently a carcinoma. Current models show that the pic ture is often very complex and di ff ers between tumours and that a simple sequence does not operate consistently . Several types of genetic abnormality can occur during tumorigenesis. The main categories of abnormalities are point mutations, fusion genes and cop y number changes. Point muta tions ar e single changes in the sequence of nucleotides in DNA and can be germline, i.e. inherited from a parent and accord ingly present in every cell in the body , or somatic, i.e. acquir at some point during life and a ff ecting only the tumour cells. Deletions and insertions (indels) of nucleotides result in a frameshift mutation. Examples include TP53 tumour suppres sor gene mutations, causing production of an abnormal p53 protein that lacks suppressor function; and mutation of the KIT gene, causing ligand-independent activation of a growth factor receptor. Fusion genes may be formed by several mechanisms, including translocations and deletions. The translocation t(14:18) in follicular

lymphoma results in juxtaposition of the anti-apoptotic BCL2 to a regulatory region of an immunoglob ulin heavy chain gene, with subsequent bcl-2 overexpression. Fusion genes can result from various chromosomal changes, e.g. TMPRSS2-ERG gene fusion in prostate adenocarcinoma can occur as a result of a chromosomal deletion and causes abnormal oncogenic activation of ERG . Gene amplification refers to an increase in copy number, resulting in overexpression of the gene, and can variably result from abnormalities in DNA replica tion, chromosomal struc ture or telomeres. An example is HER2 amplification, resulting in overexpression of the growth factor in carcinomas of breast and stomach. These many types of abnormality in the genome may ultimately interfere with the function of proteins involved in regulatory processes: TP53 and KRAS mutations are among the most common. Genetic changes can disrupt various path ways, including signal transduction (e.g. various growth factors and growth factor receptors, intracellular components such as RAS genes, APC gene), cell cycle regulators (e.g. p16 DNA repair pathways (e.g. MMR genes, BRCA1 mutations in breast carcinoma) and apoptosis (e.g. BCL2 , an inhibitor of apoptosis). DNA MMR genes play a vital role in correcting replication errors and other errors. Abnormalities of MMR genes cause instability of short tandem repeated sequences of DNA known as micr osatellites, resulting in MSI. Tumours with this char acteristic are MSI-H (high level of MSI). The relevant genes are MLH1, MSH2, MSH6 and PMS2 . MSI is a feature of around 15% of CRCs and can result either from a germline mutation in the MMR gene (Lynch syndrome) or, more often, Eric R Fearon , contemporary , Professor of Oncology , University of Michigan, Ann Arbor, MI, USA. Bert Vogelstein , b. 1949, Professor of Oncology and Pathology , Johns Hopkins Medical School, Baltimore, MD, USA. Henry Thompson Lynch , 1928–2019, Chair of Preventative Medicine, Creighton University , Omaha, NE, USA. repair gene abnormalities in tumours). in Epigenetic changes and methylation - Epigenetic factors are external to the gene sequence and can switch it on or o ff . The latter is known as epigenetic silencing - and can result from DNA methylation (addition of a methyl group to DNA), modifications of histones and RNA-associated silencing. Loss of methylation with gene activation can occur in tumours. Conversely , hypermethylation of tumour suppressor genes or of the MMR gene MLH1 can reduce or halt their - activity , favouring malignancy . - ed Genomic changes in tumours

In normal circumstances, there is precise control of the divi - sion and proliferation of human cells. For example, various growth factors influence division by binding to specific cell surface tyrosine kinase receptors, resulting in the initiation of a complex intracellular cascade of changes . Damaged - cells may undergo apoptosis, a carefully regulated process of programmed cell death. Tumours require loss of control of cell proliferation. Abnormalities of numerous genes can a ff ect proliferation and fall into facilitate tumour development. The relevant genes two main categories, i.e. proto-oncogenes (which stimulate - cell proliferation) and tumour suppressor genes (which inhibit proliferation) but the picture is not always so straightforward. Activation of proto-oncogenes by genetic changes may induce or accelerate cell proliferation, while inhibition of tumour sup - pressor genes may remove the controls that normally prevent or retard proliferation. When a proto-oncogene contributes to cancer development, it is usually known as an oncogene. Other genetic changes can also facilitate tumorigenesis. esis. The classical model for this process is the ‘adenoma– carcinoma sequence’ of Fearon and V ogelstein, whereby the accumulation of mutations such as APC , KRAS and TP53 the colorectal mucosa corresponds broadly to the transforma tion of non-neoplastic mucosa into a colorectal adenoma and subsequently a carcinoma. Current models show that the pic ture is often very complex and di ff ers between tumours and that a simple sequence does not operate consistently . Several types of genetic abnormality can occur during tumorigenesis. The main categories of abnormalities are point

mutations, fusion genes and cop y number changes. Point muta tions ar e single changes in the sequence of nucleotides in DNA and can be germline, i.e. inherited from a parent and accord ingly present in every cell in the body , or somatic, i.e. acquir at some point during life and a ff ecting only the tumour cells. Deletions and insertions (indels) of nucleotides result in a frameshift mutation. Examples include TP53 tumour suppres sor gene mutations, causing production of an abnormal p53 protein that lacks suppressor function; and mutation of the KIT gene, causing ligand-independent activation of a growth factor receptor. Fusion genes may be formed by several mechanisms, including translocations and deletions. The translocation t(14:18) in follicular lymphoma results in juxtaposition of the anti-apoptotic BCL2 to a regulatory region of an immunoglob ulin heavy chain gene, with subsequent bcl-2 overexpression. Fusion genes can result from various chromosomal changes, e.g. TMPRSS2-ERG gene fusion in prostate adenocarcinoma can occur as a result of a chromosomal deletion and causes abnormal oncogenic activation of ERG . Gene amplification refers to an increase in copy number, resulting in overexpression of the gene, and can variably result from abnormalities in DNA replica tion, chromosomal struc ture or telomeres. An example is HER2 amplification, resulting in overexpression of the growth factor in carcinomas of breast and stomach. These many types of abnormality in the genome may ultimately interfere with the function of proteins involved in regulatory processes: TP53 and KRAS mutations are among the most common. Genetic changes can disrupt various path ways, including signal transduction (e.g. various growth factors and growth factor receptors, intracellular components such as RAS genes, APC gene), cell cycle regulators (e.g. p16 DNA repair pathways (e.g. MMR genes, BRCA1 mutations in breast carcinoma) and apoptosis (e.g. BCL2 , an inhibitor of apoptosis). DNA MMR genes play a vital role in correcting replication errors and other errors. Abnormalities of MMR genes cause instability of short tandem repeated sequences of DNA known as micr osatellites, resulting in MSI. Tumours with this char acteristic are MSI-H (high level of MSI). The relevant genes are MLH1, MSH2, MSH6 and PMS2 . MSI is a feature of around 15% of CRCs and can result either from a germline mutation in the MMR gene (Lynch syndrome) or, more often, Eric R Fearon , contemporary , Professor of Oncology , University of Michigan, Ann Arbor, MI, USA. Bert Vogelstein , b. 1949, Professor of Oncology and Pathology , Johns Hopkins Medical School, Baltimore, MD, USA. Henry Thompson Lynch , 1928–2019, Chair of Preventative Medicine, Creighton University , Omaha, NE, USA. repair gene abnormalities in tumours). in Epigenetic changes and methylation - Epigenetic factors are external to the gene sequence and can switch it on or o ff . The latter is known as epigenetic silencing - and can result from DNA methylation (addition of a methyl group to DNA), modifications of histones and RNA-associated silencing. Loss of methylation with gene activation can occur in tumours. Conversely , hypermethylation of tumour suppressor genes or of the MMR gene MLH1 can reduce or halt their - activity , favouring malignancy . - ed

---

Revision #1
Created 2025-12-31 15:08:23 UTC by Omar Ayman
Updated 2025-12-31 15:08:23 UTC by Omar Ayman