Module 1: Overview of Mantle Cell Lymphoma (MCL)

START

GB: 37202
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Tutorial

Glossary terms are identified by bold, yellow text.

Learning Objectives

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Glossary

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Glossary terms are identified by bold, yellow text. Select the word to see the definition

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Clinical Connections encourage connections between the clinical content and the patient journey

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Module Overview

This module will provide you with an overview of the mantle cell lymphoma (MCL) disease state and its clinical features.

- Learning Objectives
- Definition
- Epidemiology
- Etiology and Pathogenesis
- Risk Factors
- Summary
- Progress Check

Upon completion of this module, you should be able to:

- Describe the MCL disease state, including its epidemiology, pathogenesis, and risk factors

This section will define MCL, and discuss its epidemiology, etiology and pathogenesis, as well as associated risk factors.

Upon completion of this section, you should be able to:

DEFINITION	• Define the MCL disease state
EPIDEMIOLOGY	• Describe the key epidemiologic statistics for MCL
ETIOLOGY and PATHOGENESIS	• Outline the underlying causes and mechanisms responsible for MCL
RISK FACTORS	• Identify the main risk factors for the development of MCL

Overview of MCL

Definition

As you may recall, **lymphoma** is a type of haematologic cancer of the **lymphocytes** (B cells, T cells, and natural killer [NK] cells) that typically involves the lymph nodes. There are two major types of lymphoma:[1,2]

- Hodgkin lymphoma:[3]
  - Also known as Hodgkin disease
  - Characterised by large, abnormal, granular B cells called **Reed-Sternberg cells**

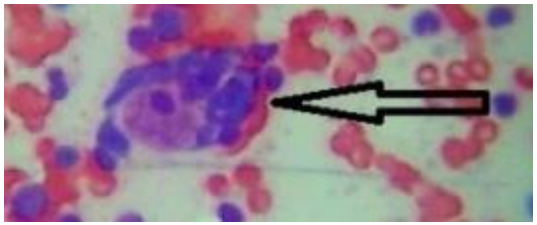

Image credit: © Szczepanek-Parulska et al.

Hodgkin lymphoma is characterised by the presence of Reed-Sternberg cells[3]

- Non-Hodgkin's lymphoma (NHL):[4]
  - Heterogeneous group of malignancies:
    - Can originate in B cells or, more rarely, in T cells and natural killer (NK) cells
    - There are over 30 subtypes of NHL[5]
  - NHL is more commonly diagnosed than Hodgkin lymphoma:[1,3]
    - NHL incidence: ~72,580 patients
    - Hodgkin lymphoma incidence: ~8500 patients

B cell T cell NK cell

NHL originates in lymphocytes[4]

Overview of MCL

Definition

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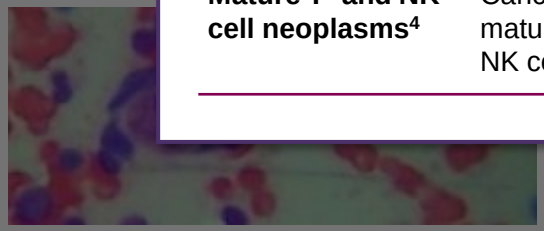
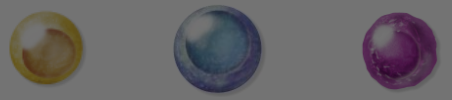


Image credit: © Szczepanek-Parulska et al.

Hodgkin lymphoma is characterized by the presence of Reed-Sternberg cells



B cell T cell NK cell

NHL originates in lymphocytes[4]

Types of NHL

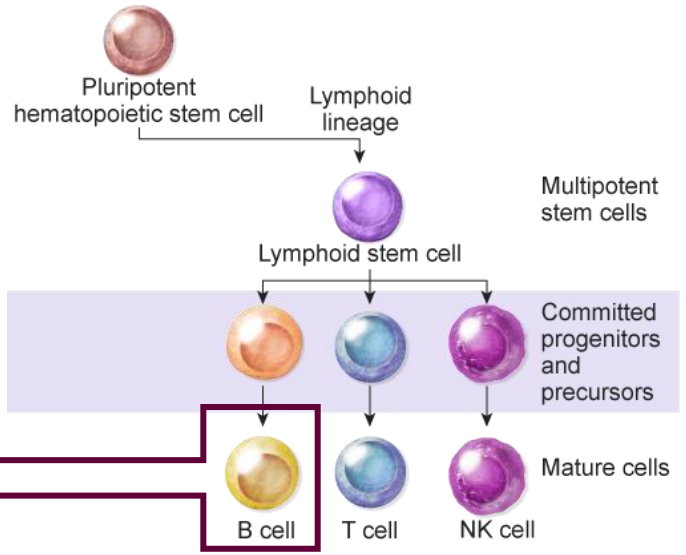
X

Lymphoma category	Description	Examples
Mature B-cell neoplasms[4]	Cancer derived from mature B cells	• Chronic lymphocytic leukaemia (CLL) • Small lymphocytic lymphoma (SLL) • Marginal zone lymphoma • Hairy cell leukaemia (HCL) • Waldenstrom Macroglobulinemia (WM) • Plasma cell myeloma • Follicular lymphoma (FL) • Mantle cell lymphoma (MCL) • Diffuse large B-cell lymphoma (DLBCL) • Burkitt lymphoma
Mature T- and NK-cell neoplasms[4]	Cancer derived from mature T cells and NK cells	• Aggressive NK-cell leukaemia • Adult T-cell leukaemia/lymphoma • Peripheral T-cell lymphoma

Overview of MCL

Definition

MCL is a subtype of NHL that originates in B cells in the mantle zone (outer edge) of lymph node follicles.[6,7]



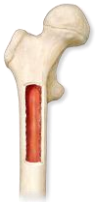
Hematopoiesis leading to the development of lymphocytes[2]

Abnormal development of B cells leads to B-cell malignancies, such as MCL.[8]

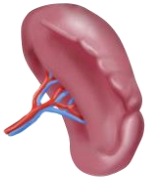
MCL is often characterised by an aggressive disease course; however, a small subset of patients have an indolent course.[4,9]

MCL typically presents with widespread involvement of the:[1,4]

Lymph nodes

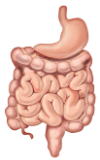


Bone marrow



Spleen

Peripheral blood



Gastrointestinal (GI) tract

Central nervous system (CNS; rare)

Overview of MCL

Definition

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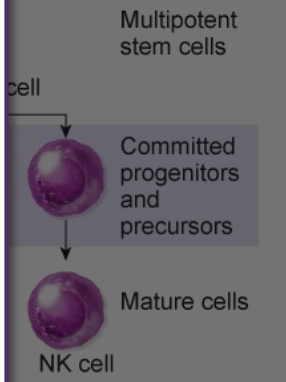

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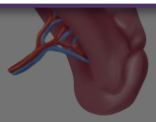
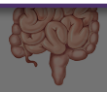
Lymph nodes

Bone marrow



Spleen

Peripheral blood



Gastrointestinal (GI) tract

Central nervous system (CNS; sometimes)

Mantle Zone

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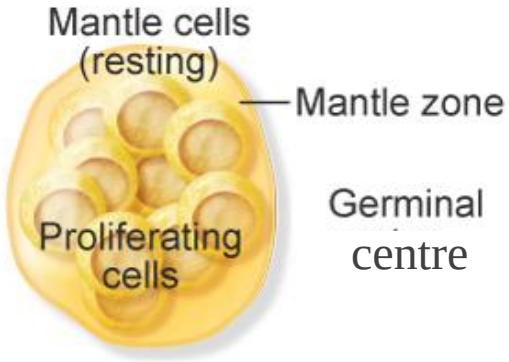
Peripheral lymphatic organs, such as lymph nodes, contain germinal centres:[10,11]

- Germinal centres consist of rapidly proliferating B cells surrounded by resting B cells along the periphery of the germinal centres—the mantle zone

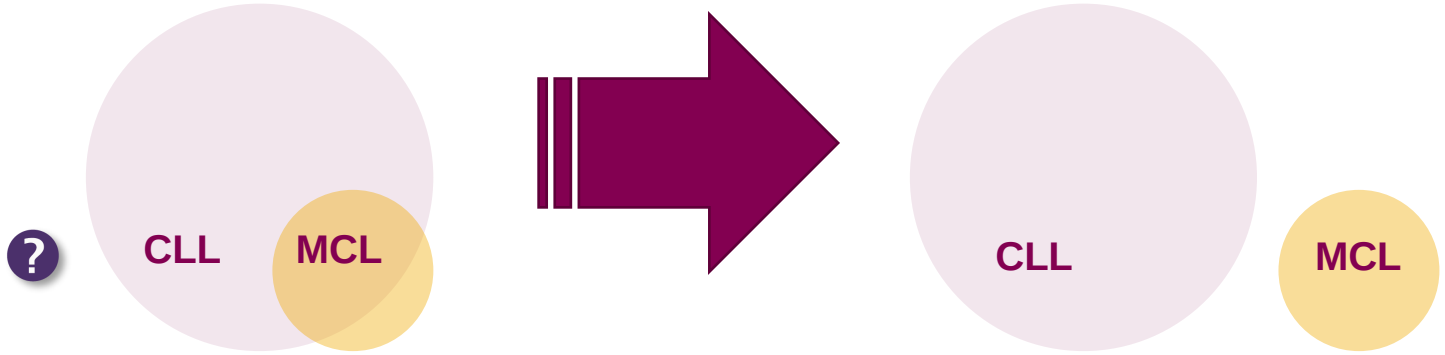


Overview of MCL

Definition

Historically, MCL was classified as CLL, and not recognised as a distinct entity.[12,13]

MCL was accepted as a distinct disease by the Revised European American Classification for Lymphoma (REAL) in 1994.[5]



- MCL is defined by the World Health Organization (WHO) as an aggressive and incurable type of mature B-cell malignancy[14]
- MCL is diagnosed and treated differently than CLL, which will be discussed in more detail later[4,15]

? MCL shares many morphologic and phenotypic features with CLL, including similar cell surface markers. Differential diagnosis is challenging but essential, since MCL is much more aggressive and requires a distinct treatment approach.[16]

Overview of MCL

Definition

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Chronic Lymphocytic Leukemia

CLL is a type of leukaemia that is characterised by the progressive accumulation of leukaemia cells in the bone marrow and blood:[8,17]

- CLL comprises about 25% of all new cases of leukaemia in the United States
- CLL derives from mature B cells that divide uncontrollably upon activation by an **antigen**

- MCL is defined by the World Health Organization (WHO) as an aggressive and incurable type of mature B-cell malignancy[13]
- MCL is diagnosed and treated differently than CLL, which will be discussed in more detail later[3,14]

MCL shares many morphologic and phenotypic features with CLL, including similar cell surface markers. Differential diagnosis is challenging but essential, since MCL is much more aggressive and requires a distinct treatment approach.[15]

Overview of MCL

Definition

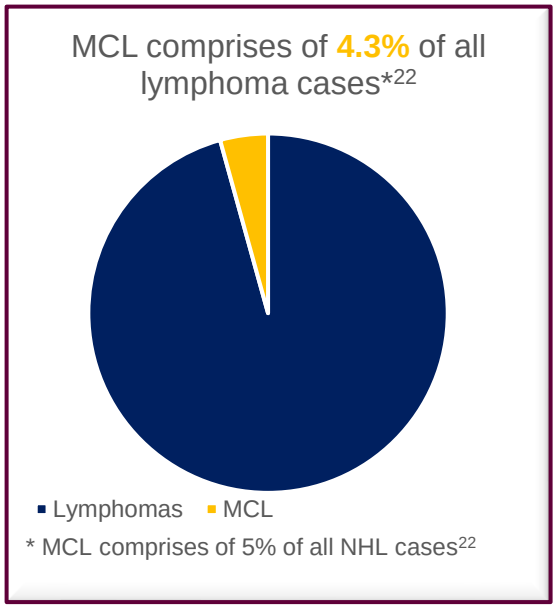
MCL vs CLL

	MCL	CLL
Incidence[18]	Average annual incidence per 100,000 – 0.9	Average annual incidence per 100,000 – 7.1
Median patient age at diagnosis[18]	71.7 years	71.6 years
Male: female ratio[18]	2.5:1	1.8:1
Site of origin[1,17]	Lymphoid tissue (eg, lymph nodes)	Bone marrow
Type of cell affected[8,17]	B cells	B cells
Type of cancer[16]	Lymphoma	Leukaemia
Survival rate for 5 years or more after diagnosis[19,20]	Around 40%	Around 85%
Common symptoms[6,17]	Unexpected weight loss, fever, drenching night sweats, enlarged lymph nodes, and pain or sense of fullness in belly	Weight loss, fever, night sweats, enlarged lymph nodes, and pain or sense of fullness in belly

Key Epidemiologic Statistics

NHL is the sixth most common cancer in the United Kingdom.[21]

14,176 new cases of NHL each year between 2016-2018 average, UK.[21]



While MCL is a relatively rare form of NHL, it can follow an aggressive disease course and is incurable.[4]

Incidence and Survival

MCL incidence was estimated by Haematological Malignancy Research Network between 2010-2016[18].

Estimated **560 cases per year in UK**[18]	Average annual incidence per 100,000[18] **0.9**
Male: female ratio[18] **2.5:1**	Survival rate for 5 years or more after diagnosis[19] **40%**

For those who are 80 or older:
around 10% of patients with MCL survive for 5 years or more.[19]

Key Epidemiologic Statistics

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Incidence and Survival

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%

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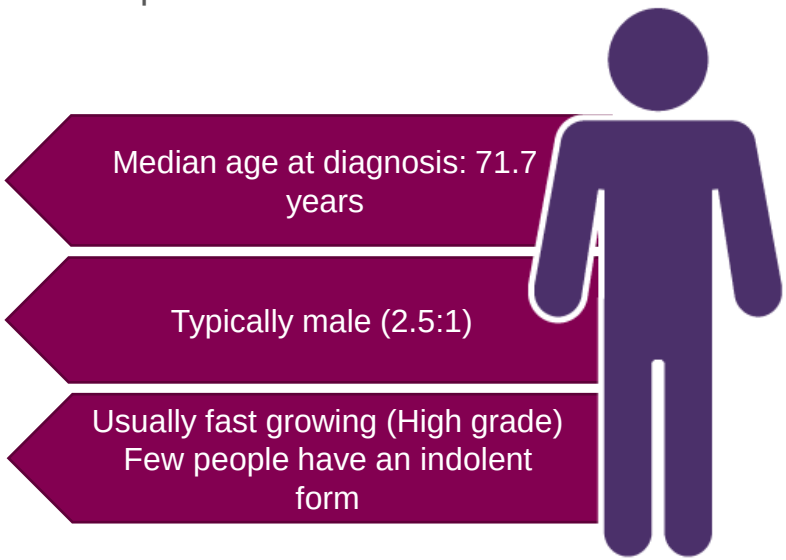
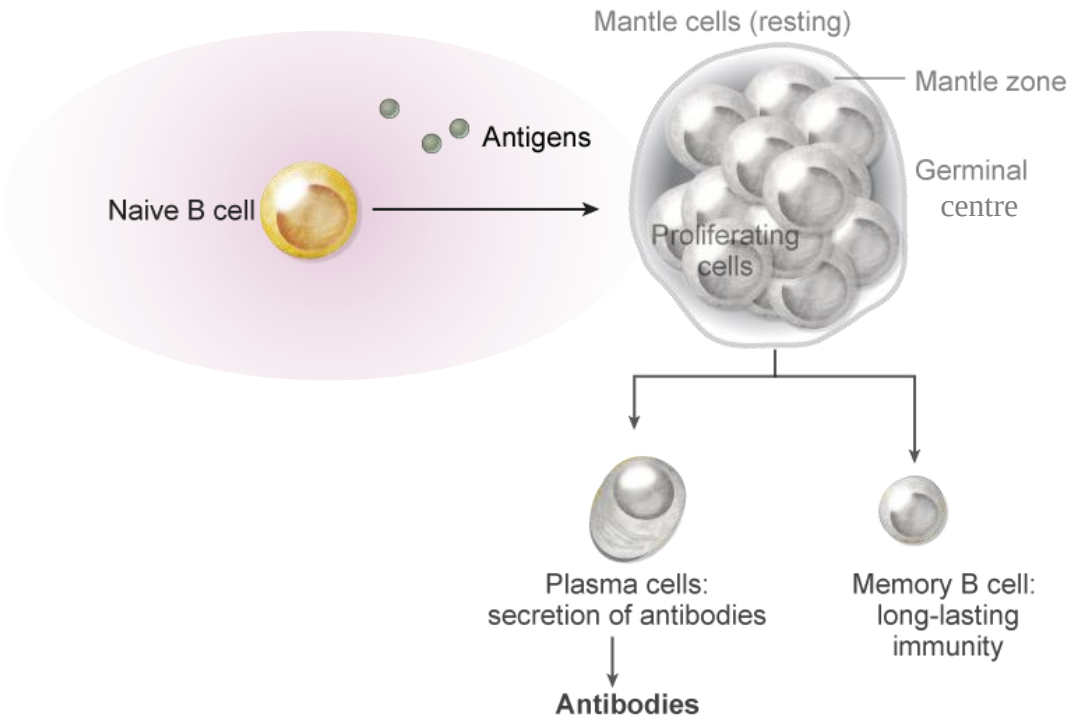
Patient Demographics

Characteristics of patients with MCL are described in the Figure.[18,23]

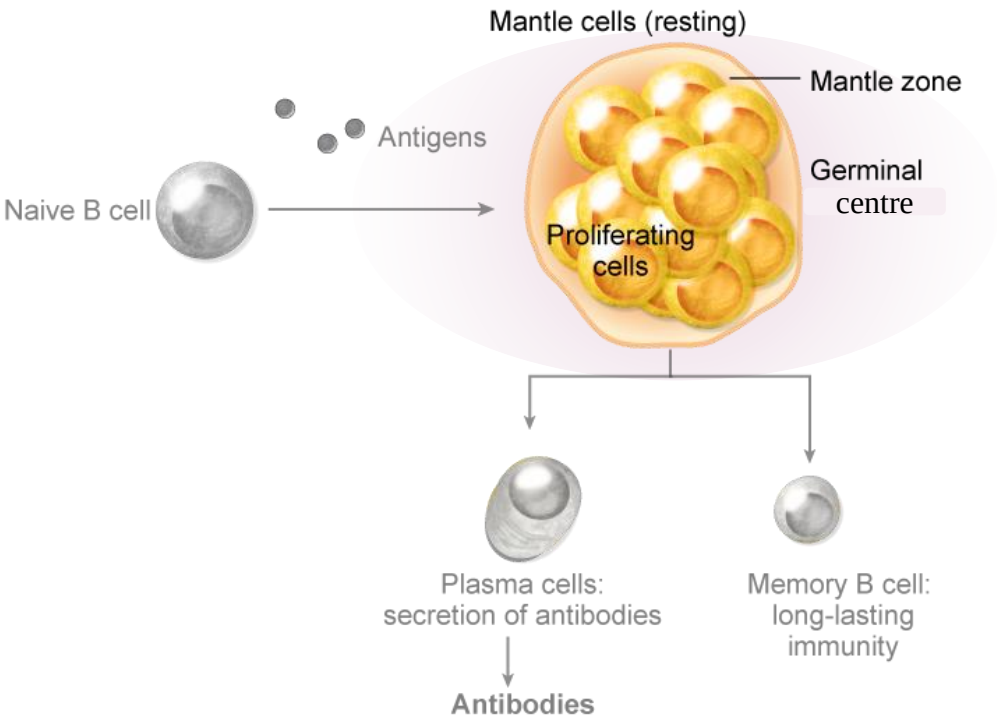


Under normal conditions, **haematopoiesis** progresses in a tightly regulated fashion to produce appropriate levels of blood cells, including B cells:[2]



Naïve B cells encounter antigens in a peripheral lymphatic organ (eg, a lymph node).[8,10,11]

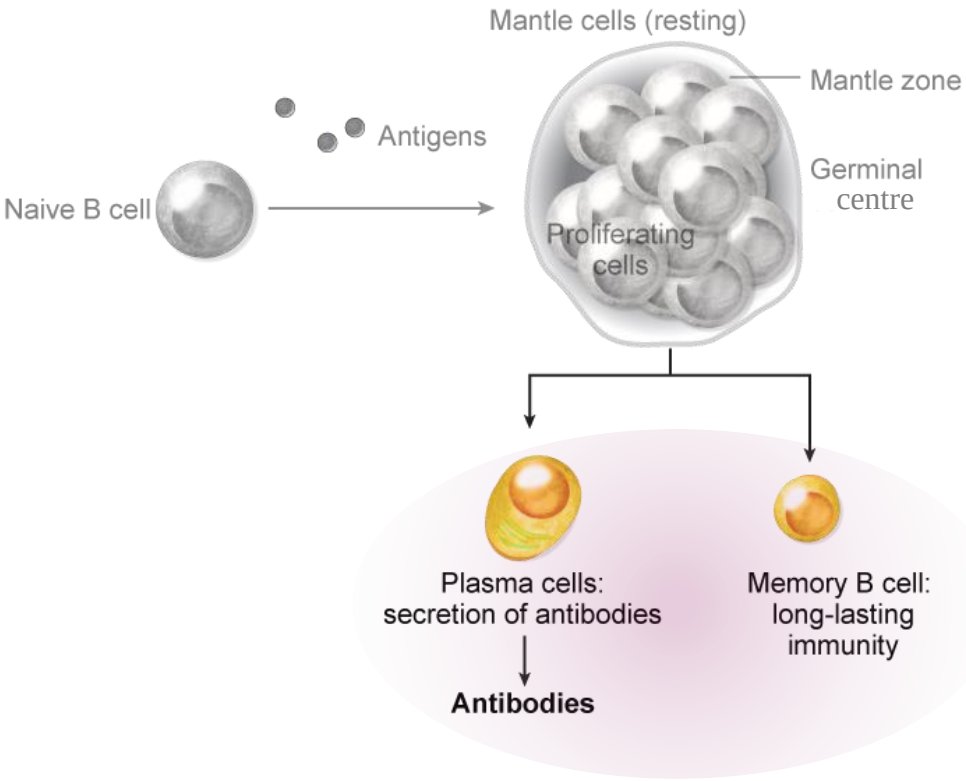
Under normal conditions, haematopoiesis progresses in a tightly regulated fashion to produce appropriate levels of blood cells, including B cells:[2]



Some B cells then enter a primary lymphoid follicle and continually proliferate to form a germinal centre, which consists of rapidly proliferating B cells surrounded by resting B cells in the mantle zone:[8,10,11]

- Within the germinal centre, B cells undergo somatic hypermutation, a process that allows B cells to mutate genes required for antibody production
- B cells are then able to produce antibodies that are better able to bind antigens (from pathogens, such as bacteria and viruses)

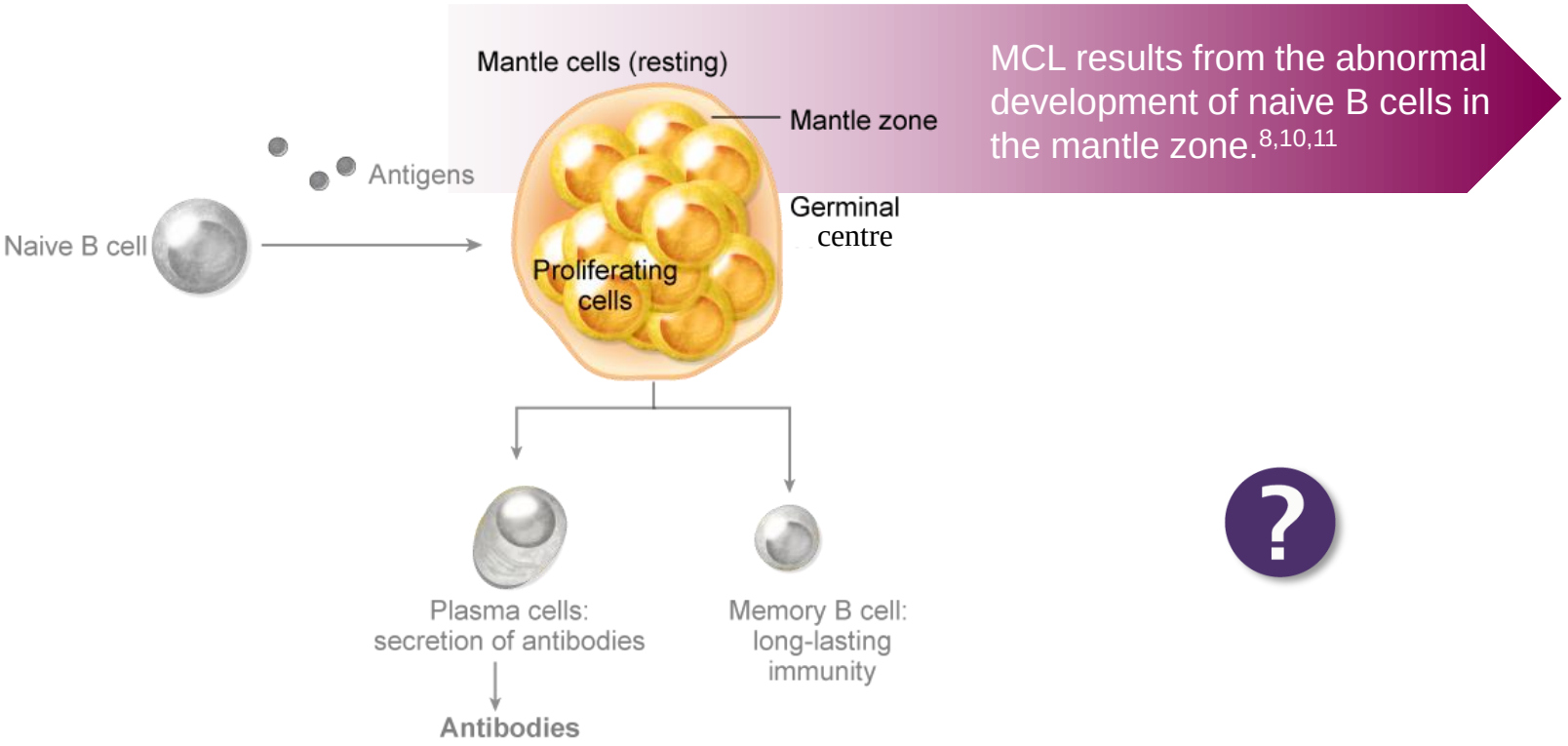
Under normal conditions, haematopoiesis progresses in a tightly regulated fashion to produce appropriate levels of blood cells, including B cells:[2]



Once activated, naive B cells can then differentiate into 1 of 2 types of activated B cells:[8,10,11]

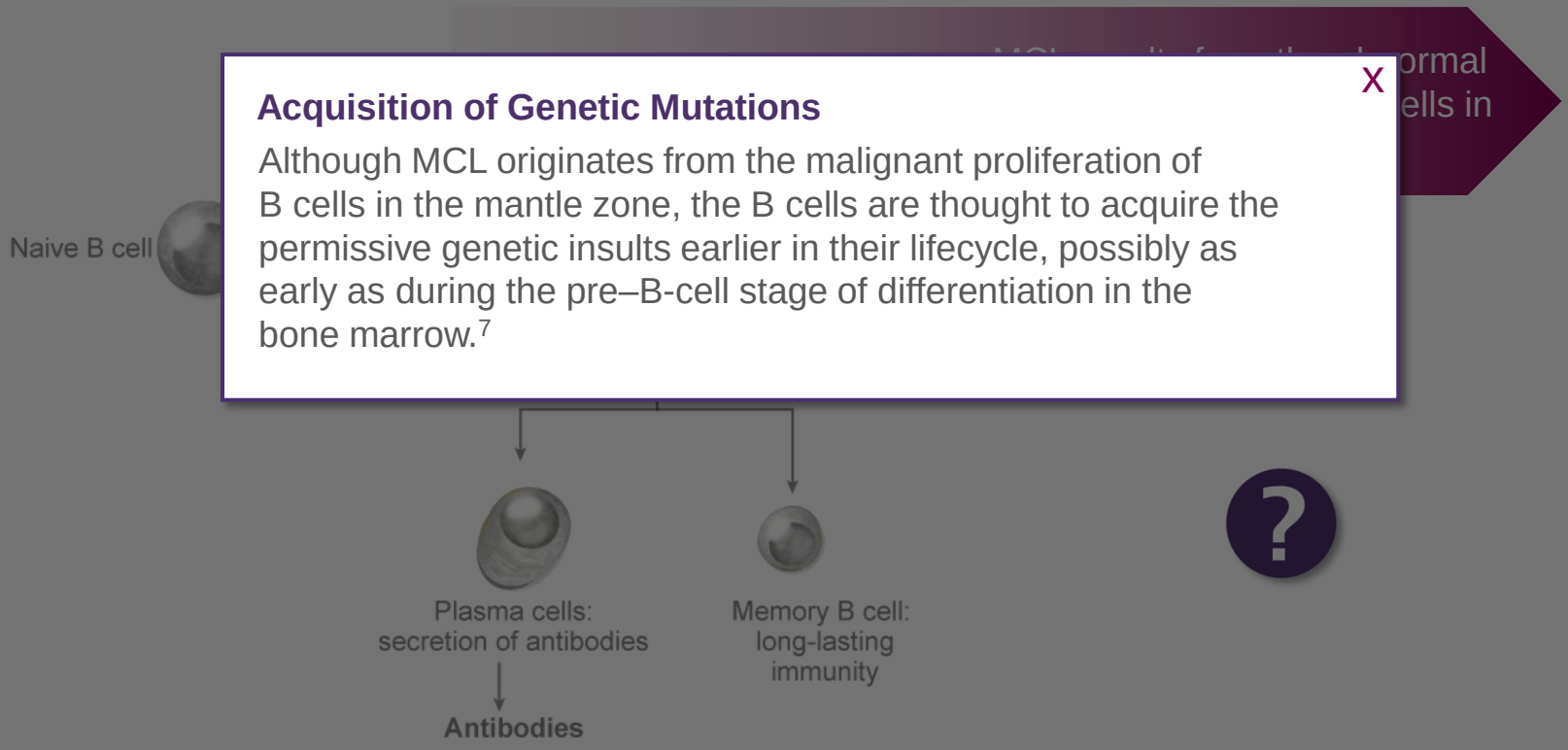
- Plasma cells, which secrete antibodies capable of binding and eliminating antigens
- Memory B cells, which mount a response in the case of subsequent exposure to their specific antigen

Under normal conditions, haematopoiesis progresses in a tightly regulated fashion to produce appropriate levels of blood cells, including B cells:[2]



MCL results from the abnormal development of naive B cells in the mantle zone.[8,10,11]

Under normal conditions, hematopoiesis progresses in a tightly regulated fashion to produce appropriate levels of blood cells, including B cells:[2]

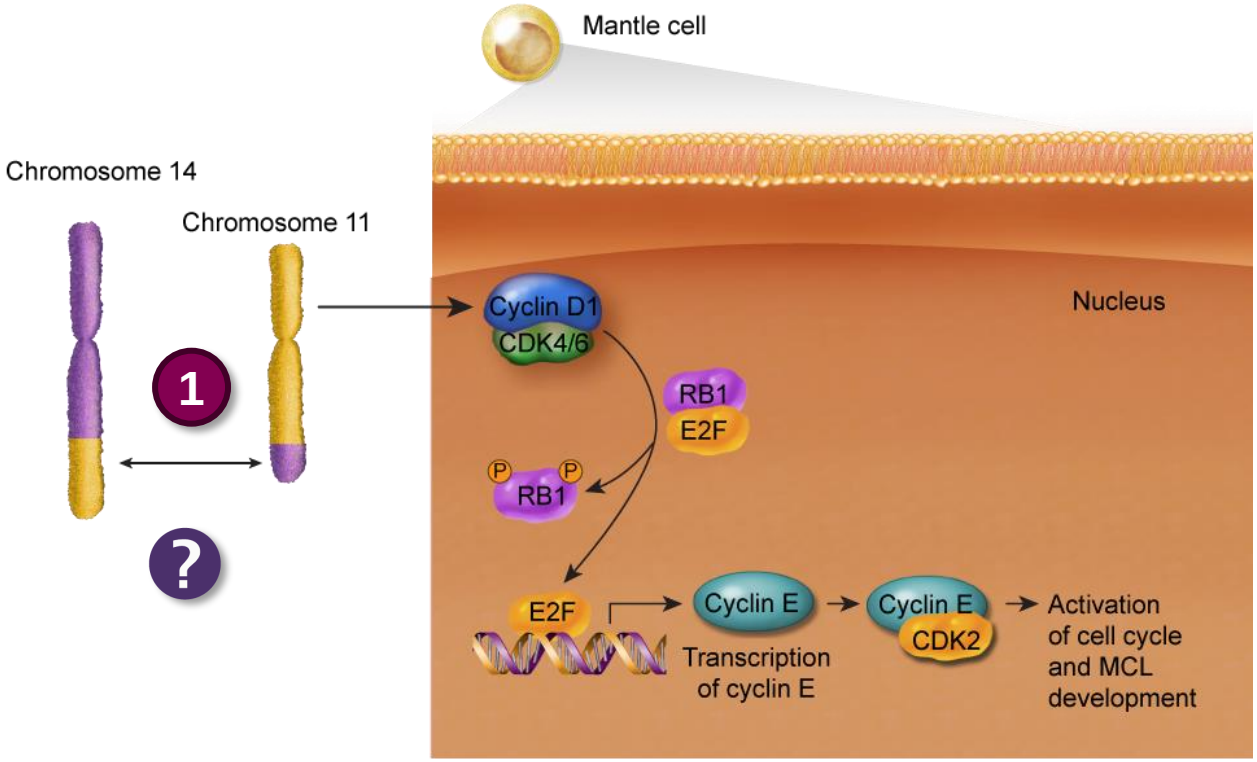


X

Acquisition of Genetic Mutations

Although MCL originates from the malignant proliferation of B cells in the mantle zone, the B cells are thought to acquire the permissive genetic insults earlier in their lifecycle, possibly as early as during the pre–B-cell stage of differentiation in the bone marrow.[7]

For MCL to develop, a cascade of molecular events leading to abnormal activation of the cell cycle and B-cell proliferation must occur.[7]



Step 1:
The t(11;14)(q13;q32) **chromosomal translocation** forms a fusion of the *CCND1* and immunoglobulin heavy chain (*IGH*) genes, leading to overexpression of the **cyclin** protein, cyclin D1.[7,24]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

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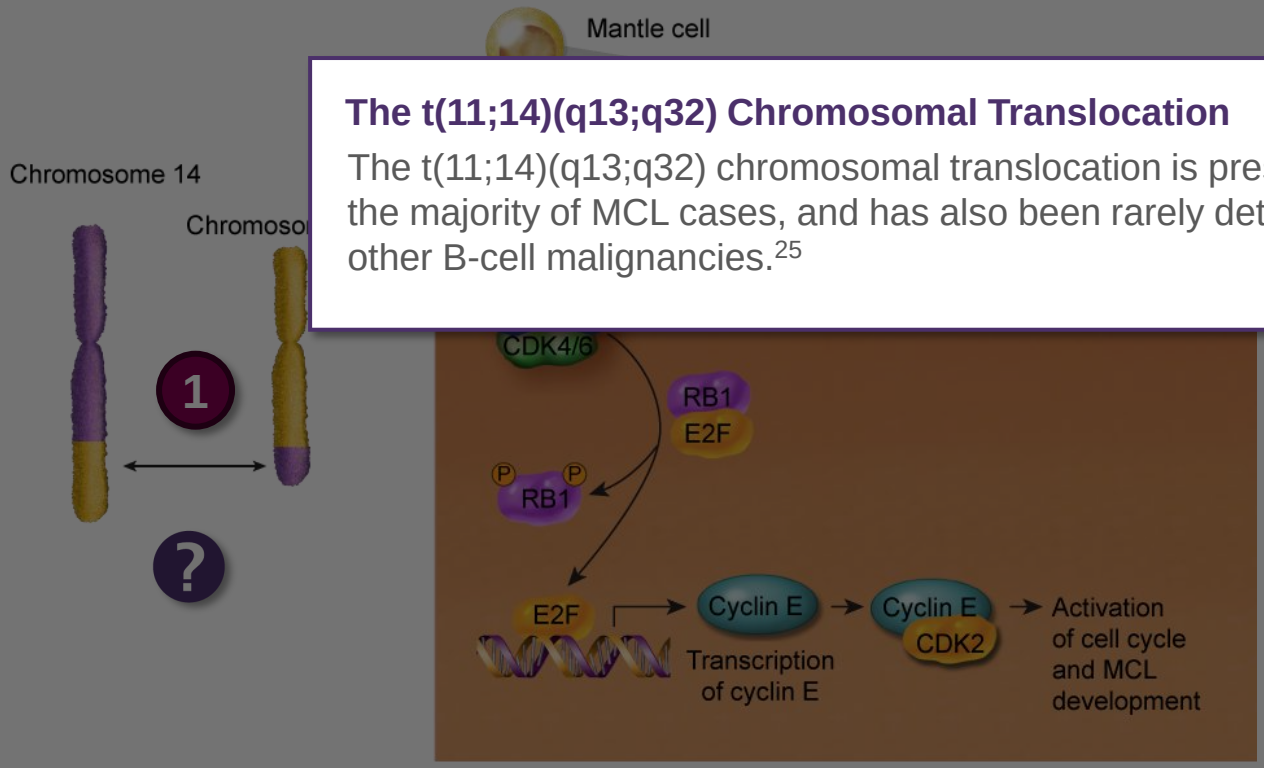

The t(11;14)(q13;q32) Chromosomal Translocation

The t(11;14)(q13;q32) chromosomal translocation is present in the majority of MCL cases, and has also been rarely detected in other B-cell malignancies.[25]

X

q13;q32) **chromosomal translocation** forms a fusion of the *CCND1* and immunoglobulin heavy chain (*IGH*) genes, leading to overexpression of the **cyclin** protein, cyclin D1.[7,24]

?

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

For MCL to de… the cell cycle and B-c…

Types of Chromosomal Abnormalities[26]

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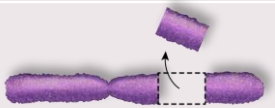
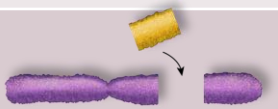
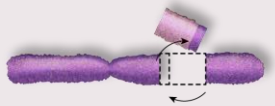
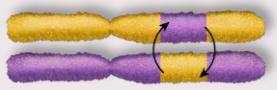
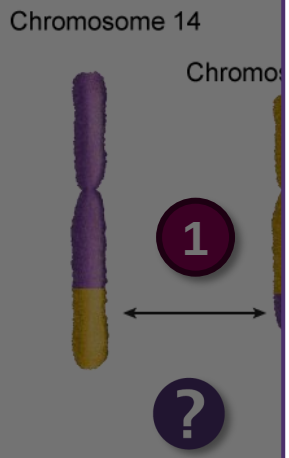
Type of mutation		Description
Point mutation		A single DNA nucleotide is changed, which may result in a change in the amino acid sequence
Deletion		Genetic material is lost
Insertion		Foreign DNA is integrated
Inversion		The DNA sequence is reversed in genes
Duplication		Multiple copies of genetic material are produced
Translocation		Genetic material is shifted between chromosomes



…13;q32)
…l translocation
…n of the *CCND1*
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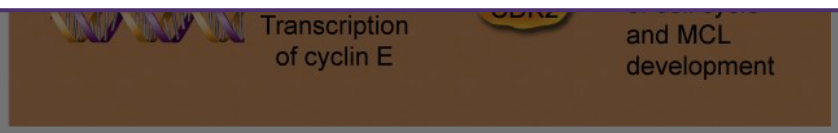
D1.[7,24]



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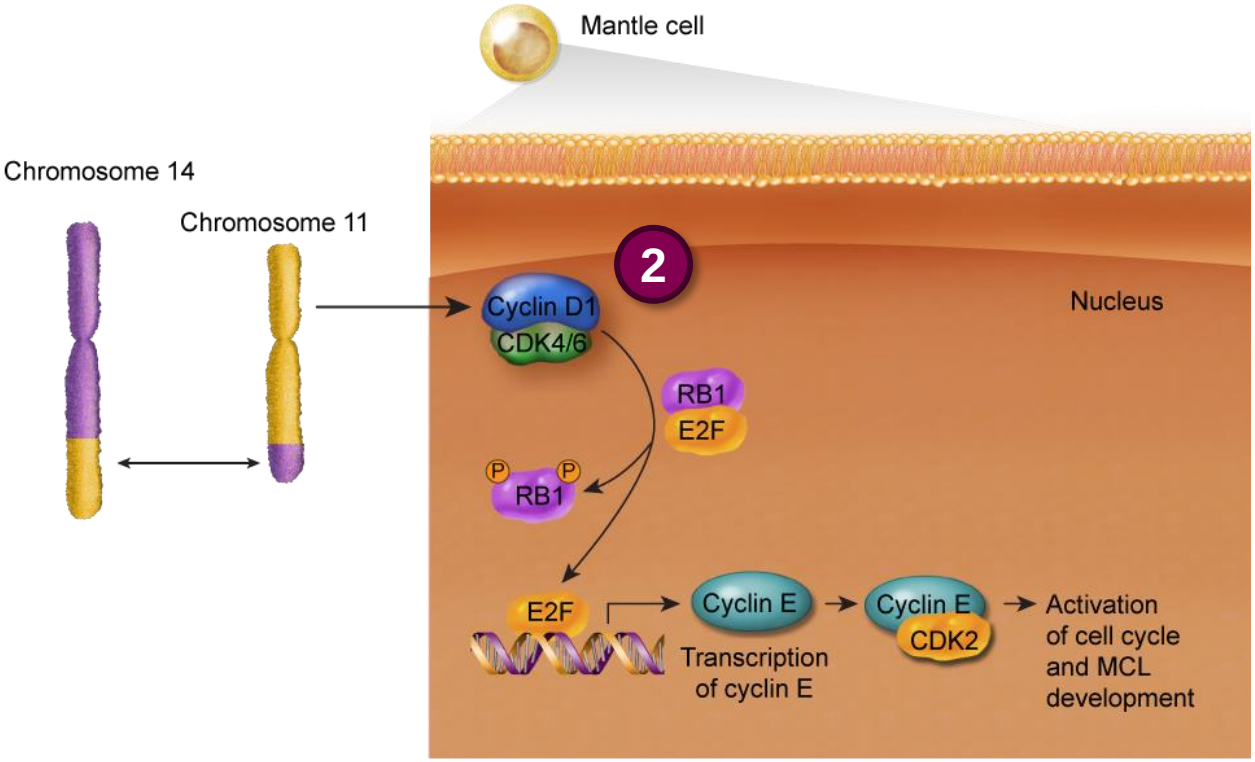
CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

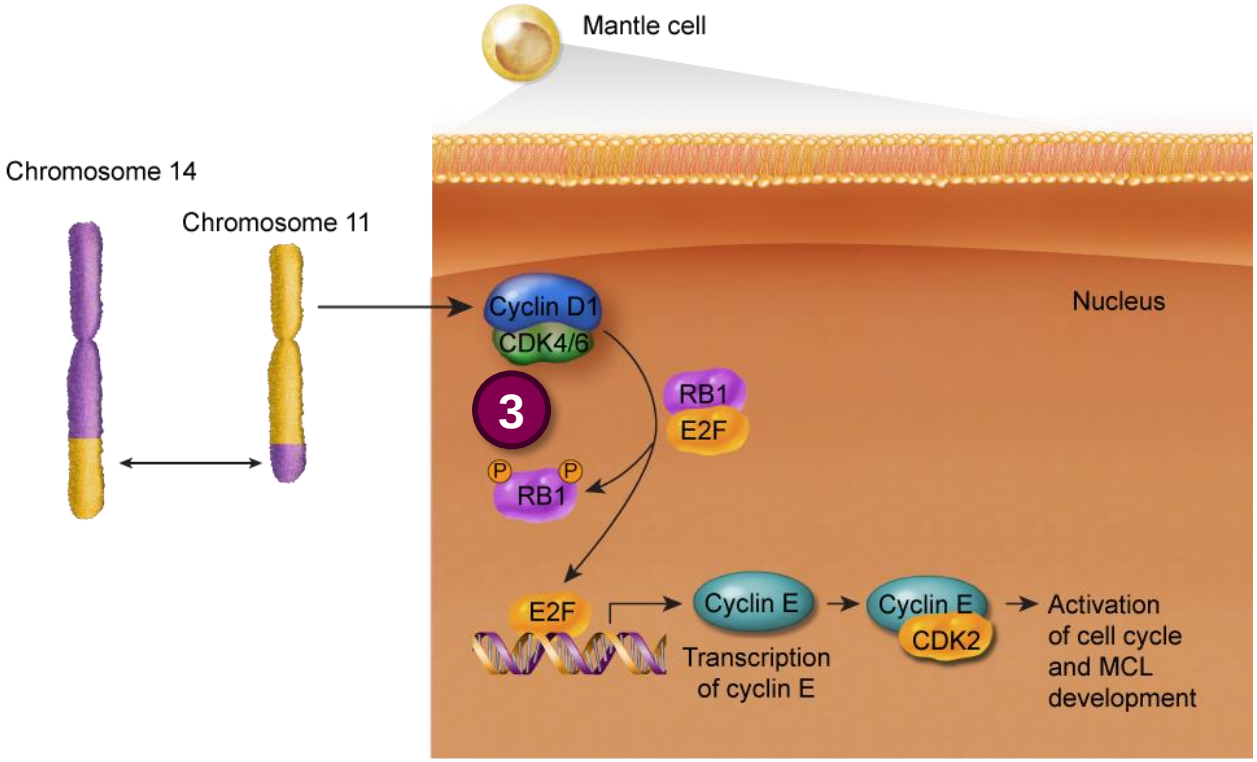
For MCL to develop, a cascade of molecular events leading to abnormal activation of the cell cycle and B-cell proliferation must occur.[7]



Step 2:
Cyclin proteins activate enzymes called cyclin-dependent kinases (CDKs), which regulate progression of the cell cycle.[7,24,27]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

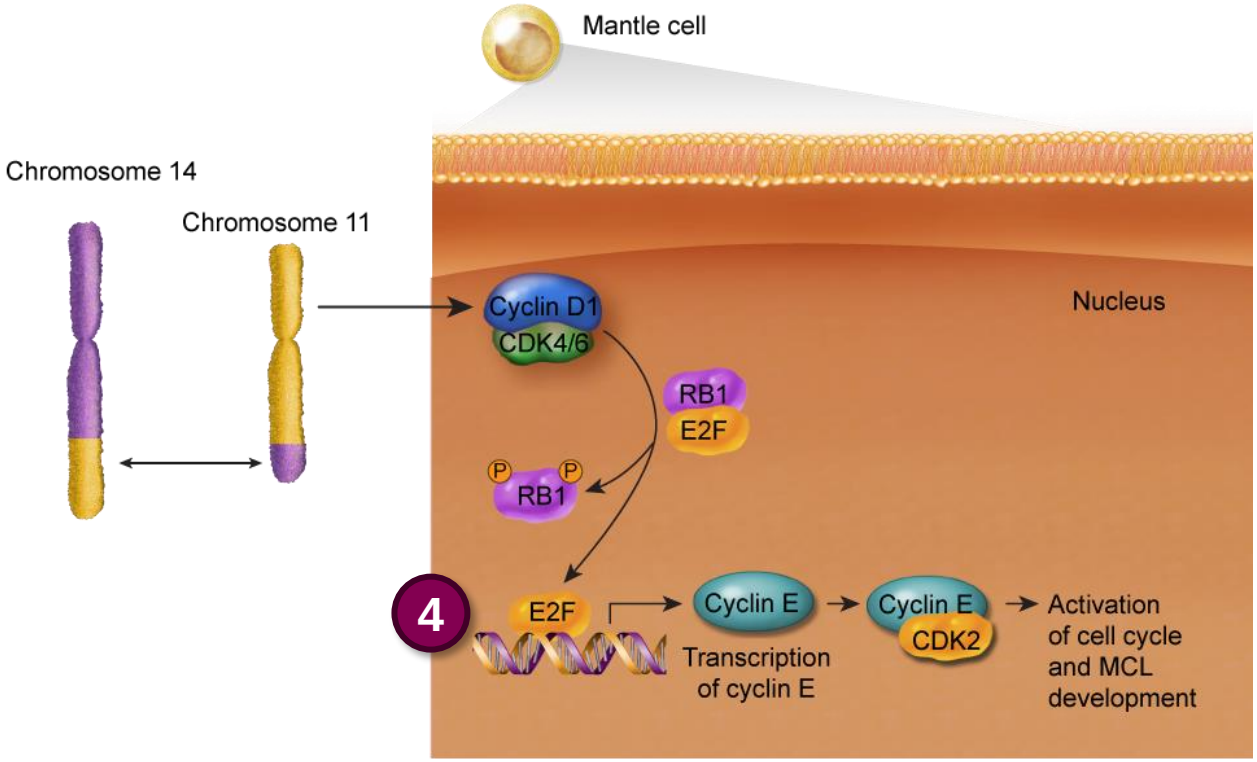
For MCL to develop, a cascade of molecular events leading to abnormal activation of the cell cycle and B-cell proliferation must occur.[7]



Step 3:
Cyclin D1 activates CDK4/6, which allows CDK4/6 to **phosphorylate** the inhibitory protein retinoblastoma 1 (RB1).[7,24]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

For MCL to develop, a cascade of molecular events leading to abnormal activation of the cell cycle and B-cell proliferation must occur.[7]



Step 4:
Phosphorylated RB1 is inactivated, releasing the transcription factor E2F.[7,24]

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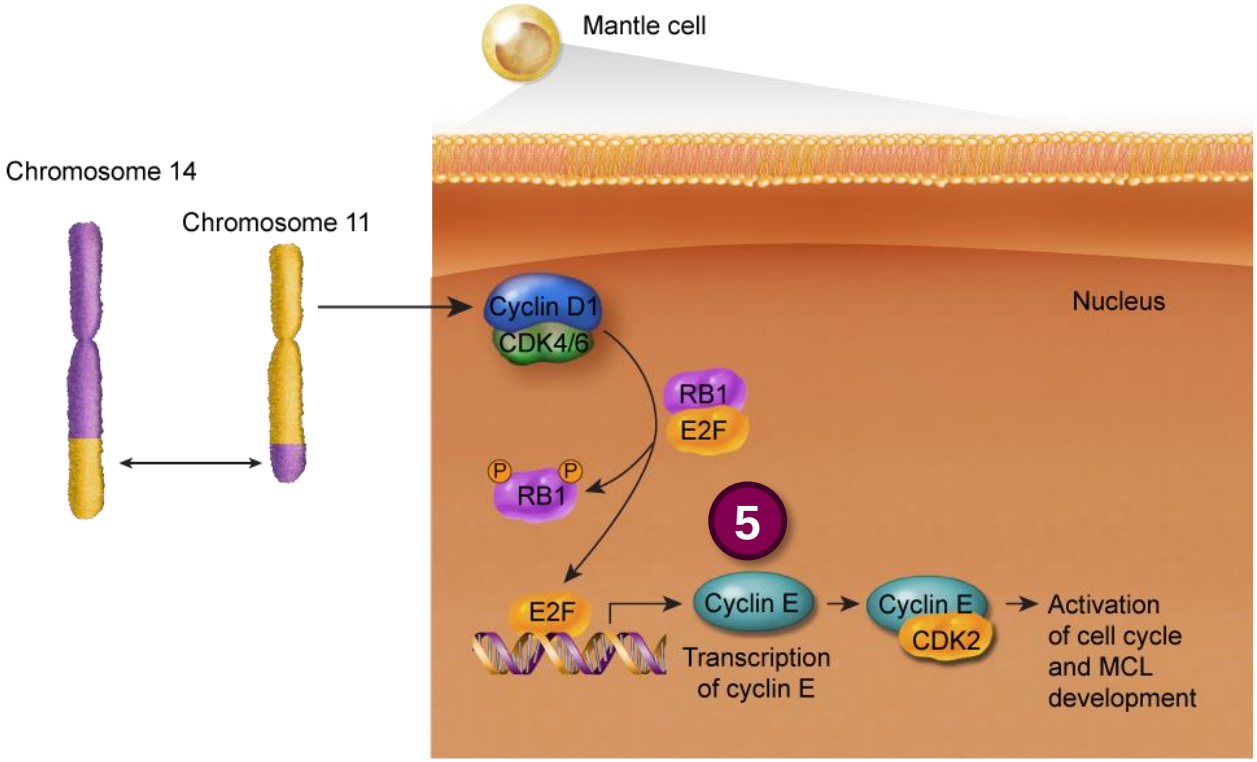

Step 5:
E2F activates the transcription of cyclin E.[7,24]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

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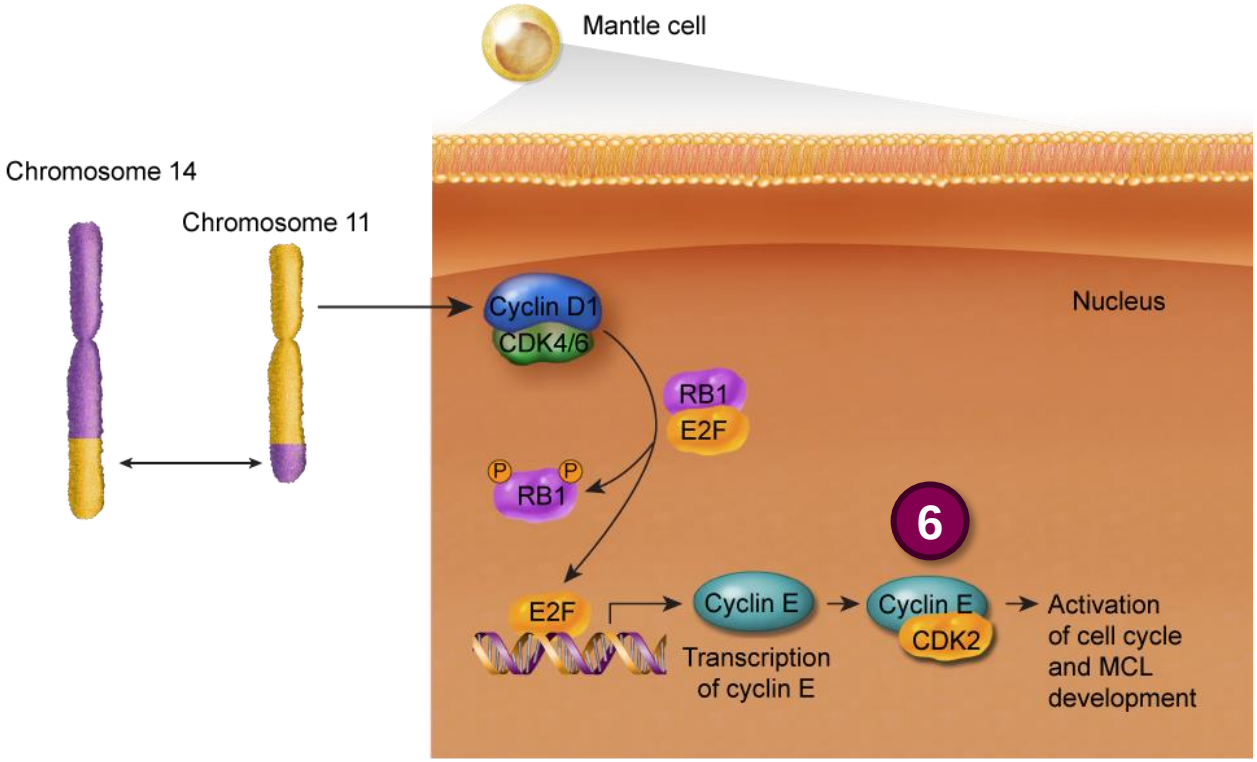
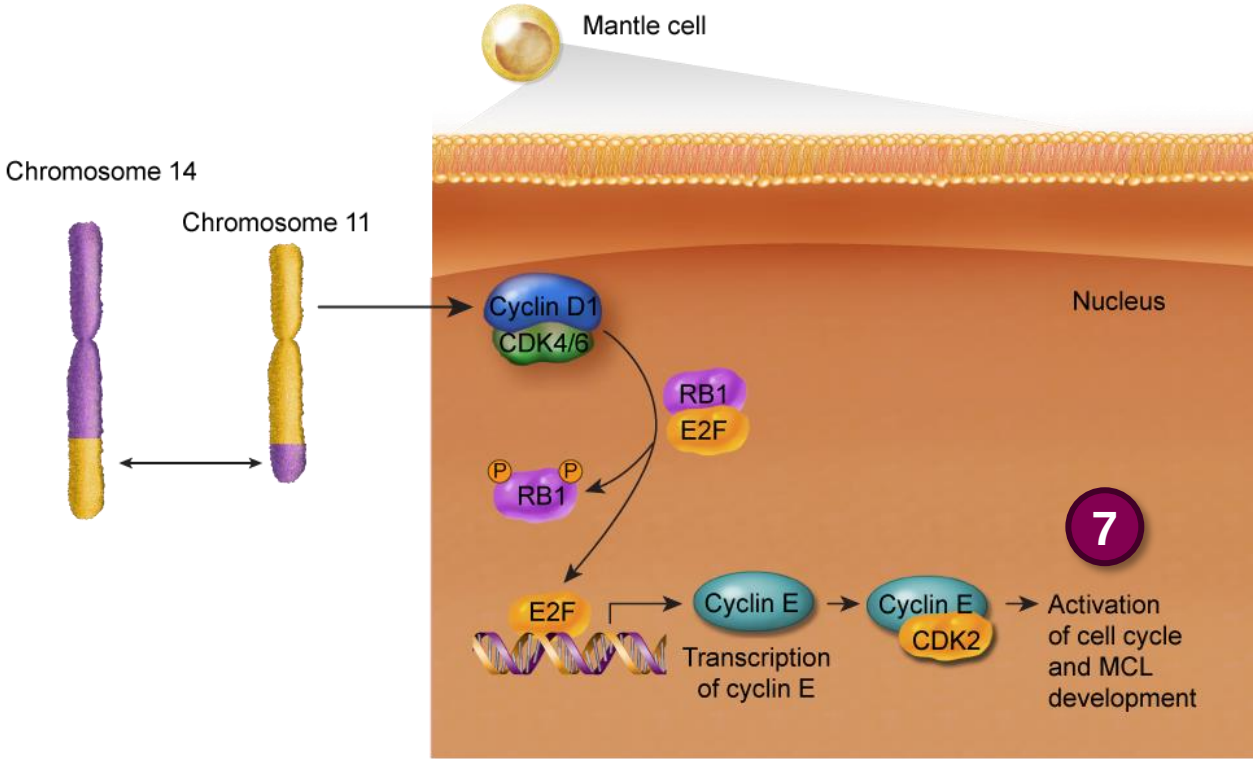


Step 6:
Cyclin E activates CDK2 and further promotes the activation of the cell cycle.[7,24]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

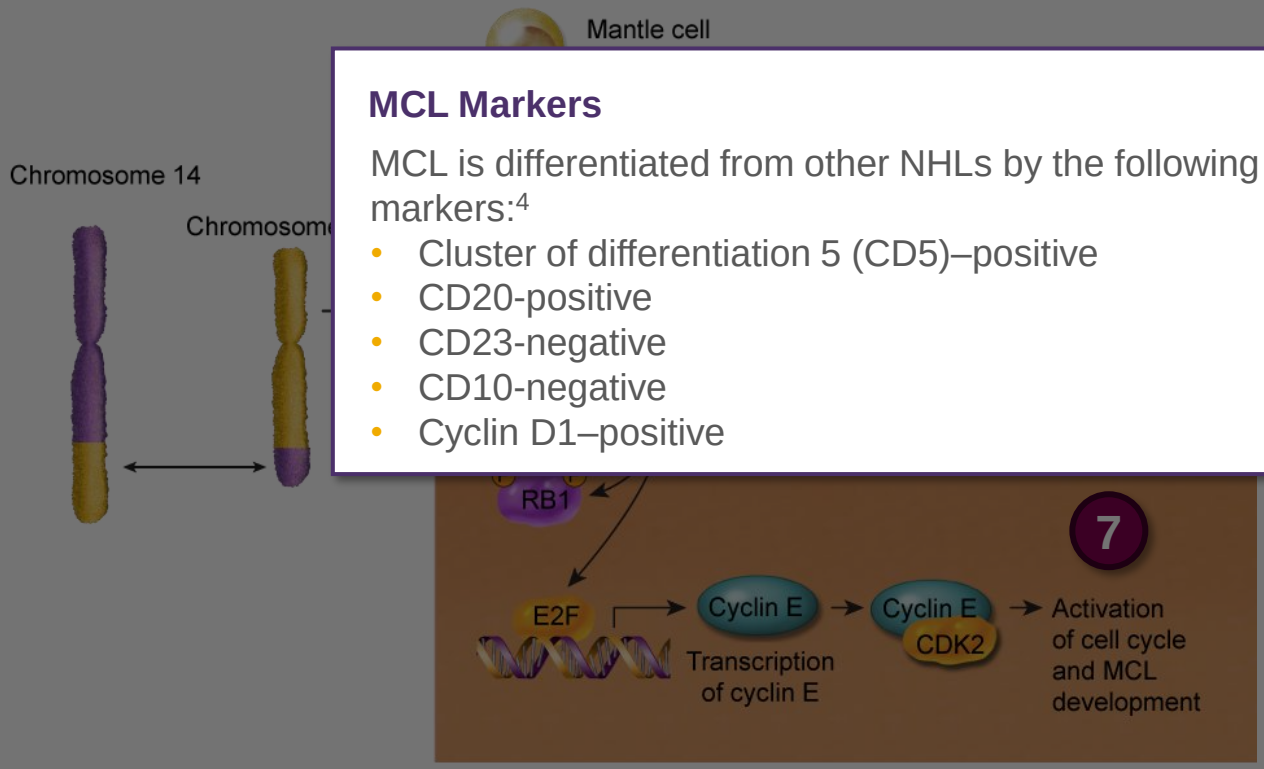
For MCL to develop, a cascade of molecular events leading to abnormal activation of the cell cycle and B-cell proliferation must occur.[7]



Step 7:
Dysregulated activation of the cell cycle promotes abnormal B-cell division and proliferation, thereby leading to MCL development.[7,24,27]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

For MCL to develop, a cascade of molecular events leading to abnormal activation of the cell cycle and B-cell proliferation must occur.[7]



MCL Markers

X

MCL is differentiated from other NHLs by the following markers:[4]

- Cluster of differentiation 5 (CD5)–positive
- CD20-positive
- CD23-negative
- CD10-negative
- Cyclin D1–positive

activation of the notes abnormal and proliferation, thereby leading to MCL development.[7,24,27]

CDK: cyclin-dependent kinase; RB1: retinoblastoma 1

Secondary Mechanisms of MCL

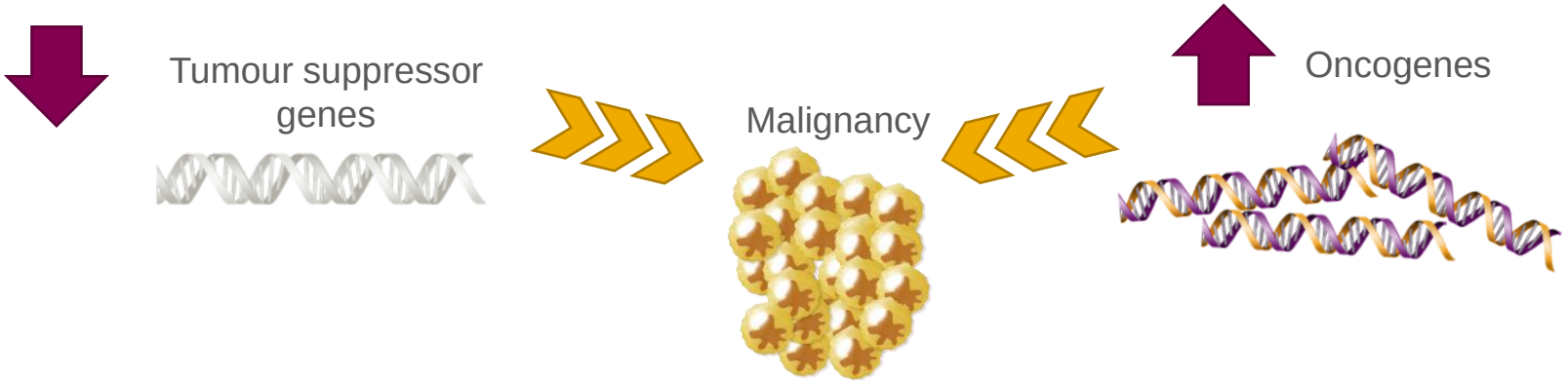
Additional molecular mechanisms may act in conjunction with cyclin D1 to further drive the growth of malignant cells and disease progression:[7]

Loss or reduction of **tumour suppressor** genes can remove inhibitory mechanisms that constrain cell growth:[26]

- Loss of function of RB1, a tumour suppressor involved in the MCL molecular pathway, is associated with more aggressive forms of MCL[28]

Gain-of-function or hyperfunction of **oncogenes** may further drive cell proliferation:[26]

- Simultaneous mutation of both oncogenes *CCND1* (encodes cyclin D1) and *MYC* (encodes a protein involved in cell cycle progression) leads to a highly aggressive and proliferative form of MCL[29,30]



Certain risk factors can increase the risk of developing NHLs such as MCL; however, since MCL is a rare disease, only a few shown here have been concretely linked to this specific subtype of NHL.[30]

Risk factor	Association
Age[30] 	Older people are more likely to develop lymphoma, with most cases occurring in people aged > 60 years
Gender[30] 	MCL occurs 2–3 times more often in men than women
Race/ethnicity[30] 	Non-Hispanic white people are more likely to develop NHLs, including MCL
Lifestyle[30] 	High body mass index (BMI), cigarette smoking, and alcohol consumption are linked to an increased risk of NHL, but have not been specifically linked to MCL
Environmental Exposure[31,32] 	Occupational exposure to herbicides and solvents is linked to the development of B-cell lymphomas such as MCL
Infection[33,34] 	Current or prior history of infection with European strains of the spirochete (bacteria that can be found in the water and soil) ***Borrelia burgdorferi*** has been linked to an increased risk of MCL
Family history[35] 	A family history of haematopoietic malignancies has been linked to a 2-fold increased risk of MCL

Overview of MCL

Summary

DEFINITION	• NHL is 1 of 2 main types of lymphoma • MCL is a form of NHL characterised by an aggressive disease course and typically widespread systemic involvement of the lymph nodes, bone marrow, spleen, peripheral blood, GI tract, and sometimes the CNS
EPIDEMIOLOGY	• MCL comprises approximately 5% of all NHL cases • 560 estimated cases per year in UK • 0.9 cases per 100,000 average incidence • MCL is predominantly diagnosed in older, male patients
ETIOLOGY and PATHOGENESIS	• MCL results from abnormal development of naive B cells in the mantle zone of lymph node follicles • Abnormal B-cell development is driven by the t(11;14)(q13;q32) chromosomal translocation leading to cyclin D1 overexpression • Overexpression of cyclin D1 triggers a molecular cascade that leads to dysregulated activation of the cell cycle, abnormal B-cell division and proliferation, and development of MCL
RISK FACTORS	• Risk factors specifically linked to MCL remain relatively unknown because the disease is rare • Prior infection with *Borrelia burgdorferi* as well as exposure to herbicides and solvents have been linked to an increased risk of MCL

1. MCL arises from the uncontrolled growth of what type of lymphocyte?

A) Astrocytes

B) B cells

C) Natural killer (NK) cells

D) T cells

1. MCL arises from the uncontrolled growth of what type of lymphocyte?

A) Astrocytes

B) B cells

C) Natural killer (NK) cells

D) T cells

B) MCL arises from the malignancy of B cells in the mantle zone of lymphatic organs.

2. Which of the following statements is true about the epidemiology of MCL?

A) Accounts for 60% of all forms of non-Hodgkin's lymphoma (NHL)

B) Median age at diagnosis is 71.7 years

C) More common in men of African descent

D) More common in women

2. Which of the following statements is true about the epidemiology of MCL?

A) Accounts for 60% of all forms of non-Hodgkin's lymphoma (NHL)

B) Median age at diagnosis is 71.7 years

C) More common in men of African descent

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B) The median age at diagnosis of MCL is 71.7 years.

3. Which of the following mutations typically triggers abnormal cell proliferation leading to MCL?

A) Deletion

B) Duplication

C) Inversion

D) Translocation

3. Which of the following mutations typically triggers abnormal cell proliferation leading to MCL?

A) Deletion

B) Duplication

C) Inversion

D) Translocation

D) MCL is characterised by a translocation between chromosomes 11 and 14.

4. MCL is initiated by the overproduction of which of the following molecules?

A) Cyclin-dependent kinase 2 (CDK2)

B) Cyclin D1

C) Cyclin E

D) Retinoblastoma 1 (RB1)

4. MCL is initiated by the overproduction of which of the following molecules?

A) Cyclin-dependent kinase 2 (CDK2)

B) Cyclin D1

C) Cyclin E

D) Retinoblastoma 1 (RB1)

B) MCL is characterised by the overexpression of cyclin D1, which triggers a molecular cascade that leads to activation of the cell cycle and B-cell division and proliferation.

5. Which of the following is a risk factor for the development of MCL?

A) Female gender

B) Hepatitis C virus (HCV) infection

C) Low body mass index (BMI)

D) Older age

5. Which of the following is a key risk factor for the development of MCL?

A) Female gender

B) Hepatitis C virus (HCV) infection

C) Low body mass index (BMI)

D) Older age

D) Older age is a key risk factor for the development of MCL.

Glossary

Select the definition to return.

Antigen

A substance capable of eliciting an immune response or binding with an antibody. Cell surface antigens mark and identify cells as self or nonself.[34]

Borrelia burgdorferi

A bacteria that causes Lyme disease.[34]

Chromosomal translocation

A mutation involving the attachment of part of a chromosome to a different chromosome.[27]

Cyclin

A protein that activates CDK enzymes to regulate the progression of the cell cycle. Cyclin protein concentrations within the body fluctuate according to the cell cycle.[27]

Haematopoiesis

The formation of blood cells, which occurs in the red bone marrow.[2]

Leukaemia

A group of cancers in which abnormal white blood cells multiply uncontrollably.[2]

Lymphocyte

A type of white blood cell that has several functions in the immune system. Lymphocytes include T cells, B cells, and natural killer cells.[2,34]

Lymphoma

A group of cancers that originates in the lymphocytes.[6]

Oncogene

A mutated form of a gene that normally controls cell growth or division; its activation can promote malignancy.[27]

Phosphorylate

The addition of a phosphate group to an organic compound.[34]

Reed-Sternberg cell

An abnormal type of B cell that is larger than normal lymphocytes. Reed-Sternberg cells look different from other non-Hodgkin's lymphoma cells.[3]

Tumor suppressor

A gene that functions to suppress cancer development; its inactivation can promote malignancy.[27]

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