Drugs Against Cancer: Stories of Discovery and the Quest for a Cure

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CHAPTER 33

The retinoblastoma story – control of cell division.

The story dates back to 1657 with the description of a large tumor in the left eye of a 3-year old child by Petrius Pawius, a Professor of Anatomy in Leiden, the Netherlands (Albert, 1987). His description of the tumor as "filled with a substance similar to brain tissue mixed with thick blood and like crushed stone" likely was what is now called a retinoblastoma. The next mention of an eye tumor of this kind did not appear until 1767 in an article published in *Medical Observations and Inquires* entitled "The Case of a Diseased Eye Communicated to Mr. William Hunter by Mr. Hayes, Surgeon," which described a tumor in both eyes of a 3-year-old girl (Albert, 1987). We will see why sometimes there is a tumor in only one eye and sometimes in both eyes.

Retinoblastoma as a disease entity was described at last in 1809 by the colorful Scottish surgeon and ophthalmologist James Wardrop (Figure 33.1) “to bring under one general view a considerable number of facts, the greater part of which are to be found insulated and not arranged in the works of different authors-and also to describe the disease in particular organs where it has not been hitherto known to exist." Wardrop's meticulous dissections led him to conclude that the tumor in the eyes of children usually arose from the retina. His drawings and clinical descriptions accurately reflected the clinical course of the disease, including the extension of the tumor to the optic nerve and brain, as well as to metastases to different parts of the body (Albert, 1987).

The next major event in the story was the invention of the ophthalmoscope in 1851 by the famous German physicist Hermann von Helmholtz ((Helmholtz, 1951); a centennial article published in the AMA Archives of Ophthalmology). This allowed the doctor to see the retina in the living patient and thus to diagnose tumors early enough to save the patient’s life by removing the eye (Figure 33.2). Before the advent of anesthesia, this was of course a horrendously painful procedure that sometimes made doctors resort to drastic measures,

such as bleeding the patient to the point of unconsciousness (from which the patient eventually recovered). Wardrop was already convinced in 1809 that earlier removal of the eye could be life-saving (even though all his patients died from recurrence of the tumor and the procedure was for many years controversial): "… were I in any case to be assured of the existence of the disease in the early stage, I would have no hesitation in urging the performance of the operation." After chloroform became available for general anesthesia and the ophthalmoscope for early diagnosis, removal of the eye led to reports in the German literature of survival rates of 5% in 1869, 17% in 1897, and 57% in 1911 (Albert, 1987). It seems that it took much time and experience for ophthalmologists to become assured when removal of the eye was needed to save life.

When there were tumors in both eyes, one of the eyes was sometimes preserved by destroying the tumor with radiation or implanted radon seeds despite the risk of cancer developing later in life (Moore et al., 1931). Chemotherapy with intravenous nitrogen mustard or other chemotherapy was also attempted (Kupfer, 1953) but eventually abandoned.

Studying the occurrence rates of various common cancers over time, geneticists came to suspects that various cancers developed over a period of years as consequence of a sequence of several, usually between 3 and 7, mutations (Ashley, 1969). Retinoblastoma was unusual in that the cancer developed as a consequence of just 2 mutations, one in each of a diploid pair in the genome; thus only a single chromosome function needed to be defective (Knudson, 1971). The first mutation was often inherited and made the child susceptible to developing the cancer when a cell in the developing retina acquired the second mutation. It turned out that the two mutations were in the same gene, later called *RB* in the two homologous chromosomes bearing that gene (Fung et al., 1987). Thus, retinoblastoma was unique in resulting from loss of function solely of the *RB* gene. Moreover, the mutations would occur early, before the age of five, while the retina was being formed by dividing cells (retinoblasts).

Retinoblastomas were familial in about 40% of the cases, while the remainder derived susceptibility from a new mutation in a parent's germ cell or occurred during development. The mutation was in a region of a chromosome 13 (13q14), where the *RB* gene was later found to be located (Yandell et al., 1989). A mutation could then occur in the *RB* gene of the second chromosome 13 of a retinoblast cell that already had the *RB* mutation in one chromosome 13. The probability of that happening when an *RB* mutation was inherited and already present in all cells of the embryo was high enough to produce tumors in both eyes. Most familial cases, where the mutation was in the germline, had tumors in both eyes (Benedict et al., 1983).

Those cases – bilateral tumors – would occur as a function of age by so-called one-hit kinetics, because there already was one *RB* mutation in every cell and only one more would be needed to abolish *RB* function. These kinetics would be linear on a semi-logarithmic plot, as actually seen in the lower plot in Figure 33.3 (Knudson, 1971). Patients who survived inherited retinoblastoma were at risk of later developing osteosarcoma, as well as occasional other tumors, initiated by the *RB* mutations (Hansen et al., 1985).

In non-inherited cases, however, tumor development would require two mutations – one in the *RB* gene in each chromosome 13 of the same cell. This would require a sequence of two low-probability events and would show a delay, as shown in the upper curve in Figure 33.3 – which fit two-hit kinetics (Knudson, 1971). The long-term survival recently of children with the non-heritable form of the disease was 96%, whereas for the inherited form it was 90%; these high survival rates, however, were only in countries that had adequate resources and routine vision testing of children (Manrique et al., 2021).

Before the 1990's, an eye with a localized retinoblastoma tumor was sometimes saved by external beam radiation. However, patients with the inheritable form of the disease -- where there usually were tumors in both eyes, one of which was saved by radiation treatment -- would often develop new cancers later in life, because cells in every tissue already had one mutation and only a single new *RB* mutation was needed to send a cell on its way to malignancy. Radiation treatment of course increased the risk of such mutation. Patients with the non-inherited disease, on the other hand (who had a tumor in only one eye) were much less likely to develop new cancers, because their cells would need two mutations to become malignant (Figure 33.4A and 33.4B) (Eng et al., 1993).

The first sign of retinoblastoma most commonly was a white pupil noticed by a parent or pediatrician. Less commonly the first sign was strabismus (crossed eyes) or reduced vision due to the tumor obscuring the macula (central vision part of the retina). More serious eye problems in more advanced cases occurred mainly in so-called developing countries. If the tumor had already extended beyond the eyeball or had metastasized, the survival outlook was for less than one year (Manrique et al., 2021).

Chemotherapy of retinoblastoma began in the 1990's, most commonly with melphalan, etoposide, and vincristine administered intravenously. A major advance however was to administer the drugs into an artery that led into the eye. This was done by threading a catheter into the ophthalmic artery under fluoroscopic guidance and permitted many-fold higher local drug concentrations delivered directly to the eye with little or no systemic toxicity. But, if the disease had spread beyond the eye, systemic chemotherapy was needed. In early cases, where the tumor was still localized to the eye, intraarterial chemotherapy cured most patients without a great deal of toxicity and often saved the eye (Manrique et al., 2021).

Since cancers generally require mutations in several different genes before they become malignant, why was loss function of the *RB* gene sufficient to produce retinoblastomas and later sometimes osteosarcomas (or more rarely other sarcomas), but specifically those tumors? The inherited *RB* mutation would be present in other developing tissues of the embryo and infant, why don't cancers appear in those tissue as often as in the retina or bone? I don't know and it may not be known.

Figure 33.1. James Wardrop (1782–1869), the colorful Scottish surgeon and ophthalmologist who described the disease entity that came to be known as retinoblastoma. (Portrait by Andrew Geddes; from Wikipedia.) According to Wikipedia, "*Wardrop was associated with Thomas Wakley in the founding of* The Lancet *in 1823 in London, for which he first wrote savage articles and, later, witty and scurrilous lampoons in his column 'Intercepted Letters'. The letters, under the pseudonym "Brutus", were thinly disguised as by leading London surgeons, revealing their nepotism, venality and incompetence. There was enough truth in them to make the parodies sting*."

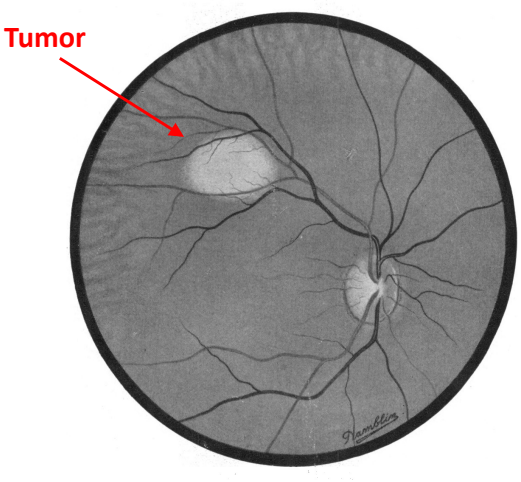

Figure 33.2. Ophthalmoscopic view of the retina with an early retinoblastoma in the eye of a child. In early cases like this, where vision was likely to be preserved, radioactive radon seeds were sometimes implanted to destroy the tumor, despite the risk of a radiation-induced cancer developing later in life (from (Moore et al., 1931) with label and arrow added). More recently, treatment of such early cases with intraarterial chemotherapy destroyed the tumor without risk of radiation-induced toxicity.

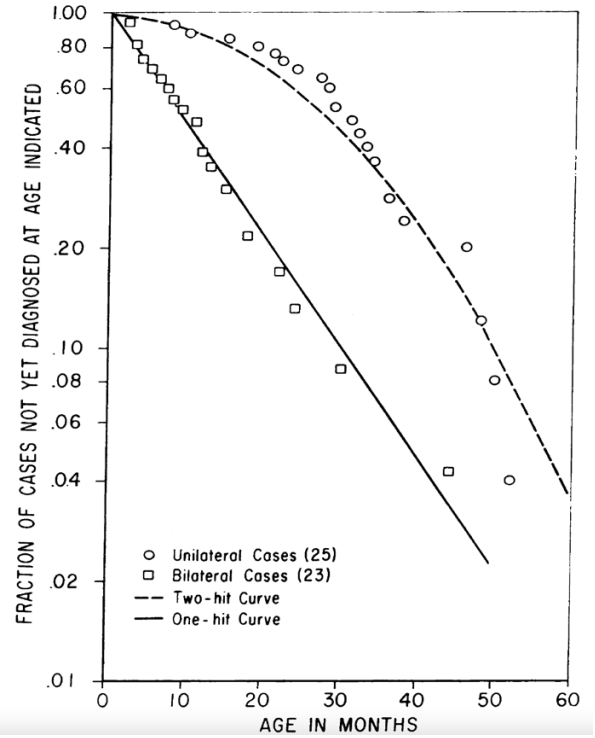

Figure 33.3. Kinetics of the development of retinoblastoma as a function of age of the child in the bilateral cases of retinoblastoma (inherited ; lower curve; one-hit kinetics) or in the unilateral cases (non-inherited ; upper curve; two-hit kinetics). See text.

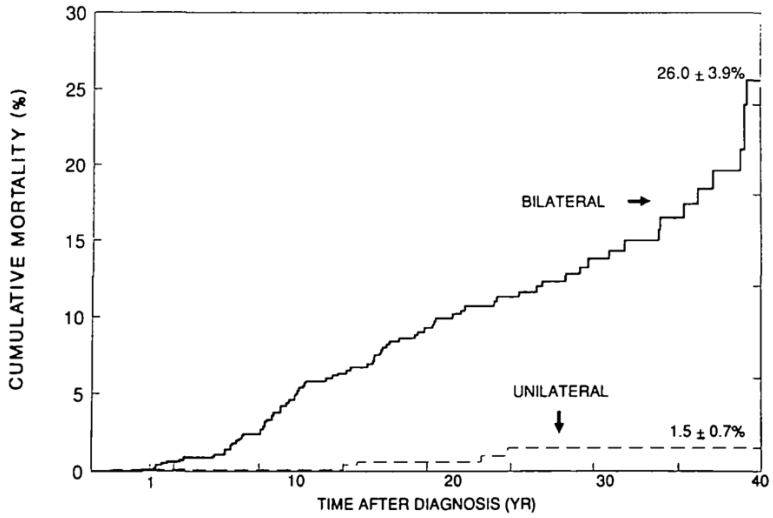

Figure 33.4A. Children with retinoblastomas in both eyes – in whom there was an *RB* mutation in the germline -- had a high risk of dying from new cancers later in life, in part secondary to eye-saving radiotherapy. Those with a tumor in only one eye had much less risk of dying later in life (Eng et al., 1993). (This was before intraarterial chemotherapy was introduced to treat early cases.)

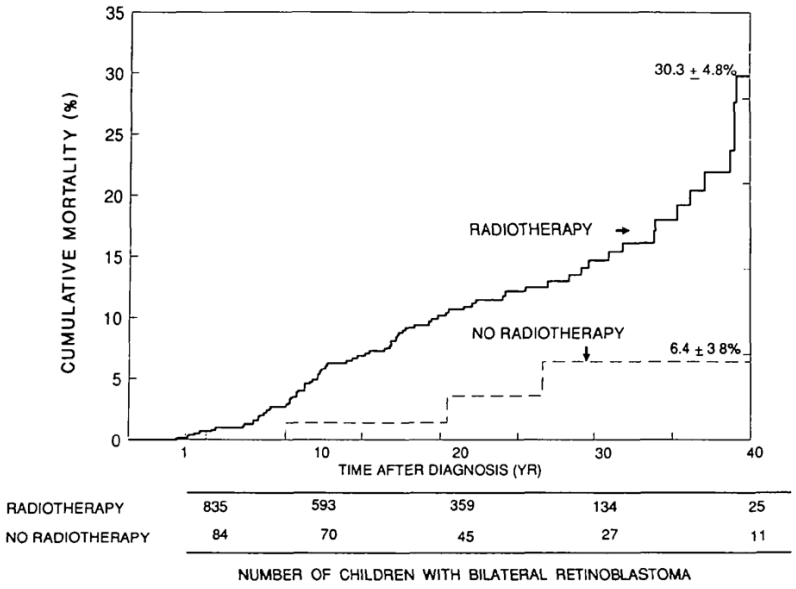

Figure 33.4B. Eye-saving radiotherapy of retinoblastoma patients increased their risk of dying later in life, usually because they developed new cancers (Eng et al., 1993).

Retinoblastoma at the pineal gland: trilateral cases.

Curiously, some inherited retinoblastoma cases are called “trilateral”! It is because these cases have, in addition to tumors in both eyes, also a tumor in the pineal gland located near the center of the brain (Figure 33.5). Among the children who have a germline mutation in the *RB* gene and retinoblastomas in both eyes, about 5% also develop a similar tumor in or near the pineal gland. Before 1995, few of these children survived, but, since then, early detection and intensive chemotherapy with stem cell rescue of the bone marrow has led to long-term survival of more than half of the children (de Jong et al., 2014).

Trilateral retinoblastoma is rare but connects with the ancient idea that the pineal was a kind of vestigial third eye. How did that idea arise, what do we know now, and why is the pineal called a gland? The name ‘pineal’, by the way, comes from the shape of the gland, which resembles a pinecone. Descartes (1594-1650) thought it to be a connection between the soul and consciousness, but this idea was soon dismissed when it was noted that many animals had a pineal yet lacked those special qualities. The notion of the pineal as a kind of third eye traces to ancient Egypt, where the pineal was considered to be the eye of Horus and to Hindu spiritual enlightenment that imagined it as an atrophied eyeball (Shoja et al., 2016). The idea of an atrophied eye may have derived from it seeming to be attached to the brain by way of a stalk. The pineal is the source of melatonin, which it secrets during the night; thus it is indeed a gland. Moreover, this light-dark dependence is functionally like what the eye does, although the gland does not respond directly to light and there seems to be no confirmed neuronal connection between the pineal and the retina. Nonetheless, the

fact that the same rare tumor type in infants occurs in both retina and pineal gland suggest a relationship in the origin of the two tissues.

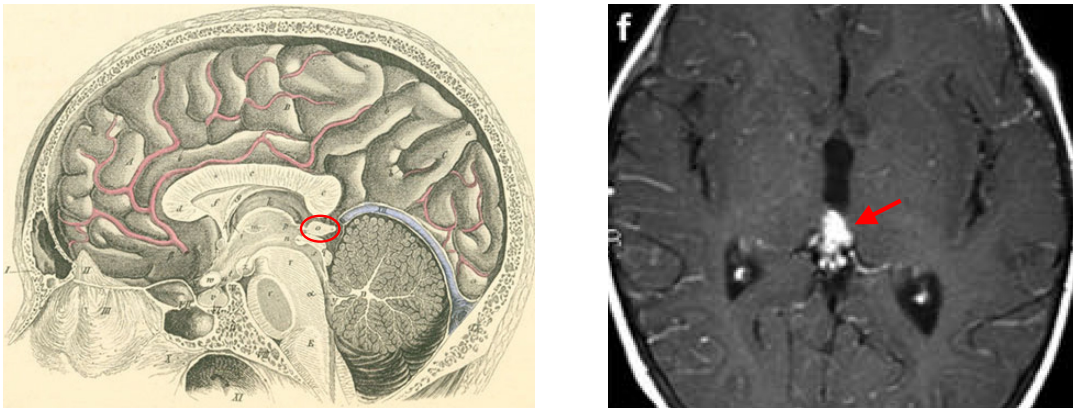

Figure 33.5. *Left*, location of the pineal gland in the center of the brain (from Bock's *Handbuch der Anatomie des Menschen* (1841) Leipzig, Germany, with red oval added). *Right*, nuclear magnetic resonance image of a retinoblastoma tumor of the pineal gland (from (De Ioris et al., 2014) with arrow added).

Cell cycle control by the Rb pathway.

Retinoblastoma tumors arise from uncontrolled growth of retinoblasts, the cells that form the retina. The uncontrolled growth is initiated by loss of *RB* gene function. *RB* is said to be a tumor suppressor gene because tumors develop when both copies of the gene, and hence hence of its protein product, pRb, are inactivated by mutation (or other process). Thus, if even one copy of a cell's pRb protein is in working condition, it suppresses the cell's likelihood of growing into a tumor. *RB* was one of the first tumor suppressor genes to be described. It was found to be a key factor (although not the sole cause, as it was in retinoblastoma) in the initiation of some of the most common cancers including those of lung, breast, and bladder. Sometimes osteosarcoma appeared without retinoblastoma; in these cases, there was also loss of *RB* gene functions, showing that both malignancies occurred by the same mechanism. After the *RB* gene was cloned, definitive evidence was obtained that the gene was a tumor suppressor. The inactivating mutation in the gene was often a point mutation – a change in only one base pair of its DNA – which did not cause a change in the chromosome that could be seen under the microscope (Benedict et al., 1990).

Aside from pRb's well-known suppression of the cell division cycle, it was also found to suppress the transcription of many genes of DNA repair and genome maintenance (Lee and Kim, 2022). Would that be useful? Speculatively, high expression of those genes in some normal cell types might entail a risk of genome derangement. High expression of those genes in pRb-deficient tumors may help tumors derived from those normal cell types – namely retinoblastomas and osteosarcomas -- to thrive (thus, possibly as an unfortunate

side effect). However, it also presented possibilities for therapy of those tumors by inhibition of the functions of one or another or several of the DNA repair or genome maintenance genes, as recently proposed by (Lee and Kim, 2022).

A critical point in the life of both normal and cancer cells is a commitment to begin DNA replication on the way to mitosis. The process begins with growth factor stimuli that in normal cells come primarily in response replication stress via RAS (Chapter 18) or via estrogen receptor, but in cancer cells come mainly in response to DNA damage via ATM or ATR (Chapter 29) (Matthews et al., 2022).

In the previous chapter, we saw that, when p53 is activated in response to ATM or ATR, it stimulates the transcription of p21cip1, which arrests the cell cycle, thereby allowing more time for DNA repair before cells start mitosis. The steps whereby p21cip1 arrests the cell cycle show the central role of the retinoblastoma gene and protein. Our understanding of those steps as of 2005 are shown in Figure 33.6, which is part of the molecular interaction map shown in Figure 32.6A of the previous chapter and in (Kohn and Pommier, 2005). The steps go from p53 to an effect on the cell cycle. But it is easier to understand it in the opposite direction. We begin with the final effect: the induced expression of genes that activate the cell cycle (action 73 in the map), which is stimulated by E2F bound to the E2 promoter of the genes (action 74). The pRb protein binds and inhibits E2F (actions 76 and 75). A Cyclin-Cdk dimer phosphorylates pRb (action 78), thereby inhibiting the binding of pRb to E2F (action 77). Finally, the activity of Cyclin-Cdk is inhibited by p21cip1 (action79), the production of the latter being enhanced by p53 (action 82). Now, tracing the steps from p21cip1 to the stimulation of the cell cycle, we see a sequence of 3 inhibitory actions (actions 79, 77, 75) – the net effect is inhibition, because a sequence of an odd number of inhibition steps yields inhibition. That is essentially how p21cip1 could inhibit the cell cycle when p53 is activated in response to DNA damage. Mdm2 was found to counter the actions of p53, consistent with its functions described in the previous chapter. Mdm2 induced the degradation of p21cip1 (actions 80 and 81) and inhibited the binding of pRb to E2F (actions 83 and 84). Both of these actions of Mdm2 would counter the p53-induced cell cycle inhibition. All of this was a plausible but simplistic yet instructive narrative -- but as often happens as knowledge progresses, further investigation disclosed a more complicated picture, as we shall see.

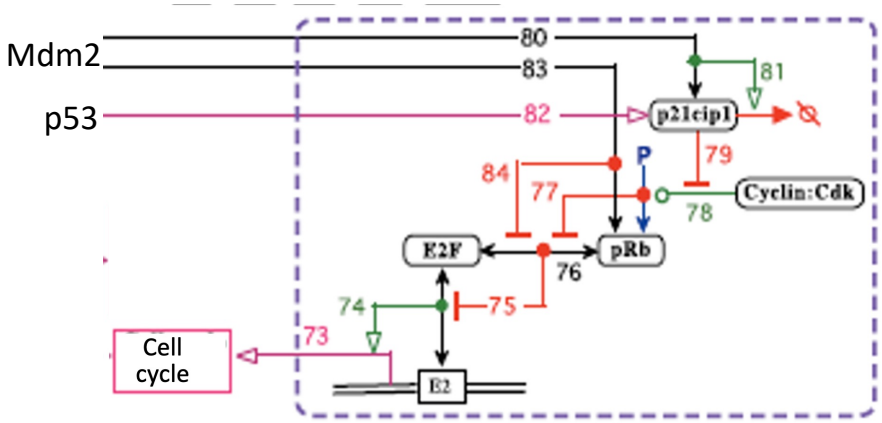

Figure 33.6. A molecular interaction map showing how p53, by producing p21cip1, inhibits the cell cycle. This happens when p53 is activated in response to DNA damage. Inhibiting the cell cycle gives more time for DNA repair before the cell begins steps to mitosis. This molecular interaction map is part of a larger map shown in Chapter 32 (Figure 32.6A) and in (Kohn and Pommier, 2005). The steps in the map are explained in the text. The symbols are defined in Figure 33.7.

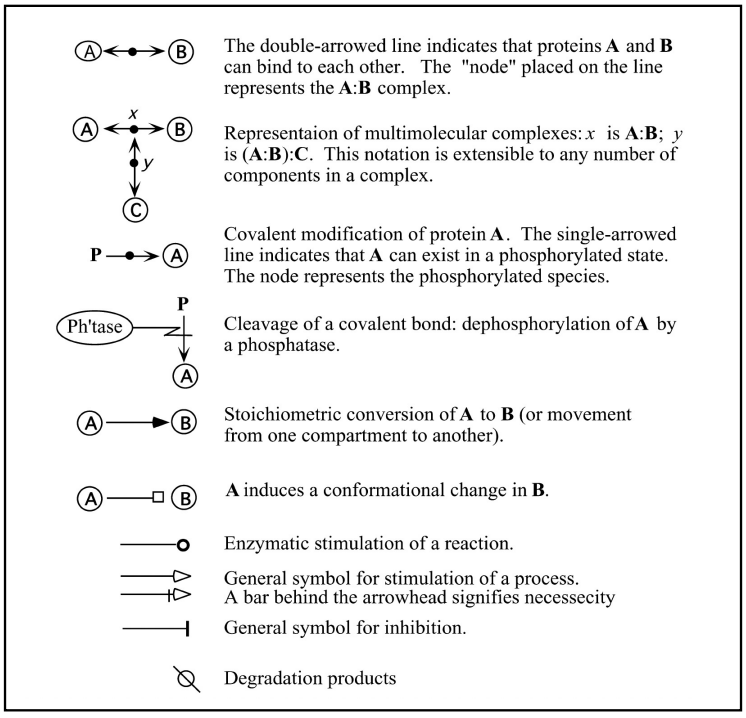

Figure 33.7. Symbol definitions for molecular interaction maps (Kohn, 1999, 2001).

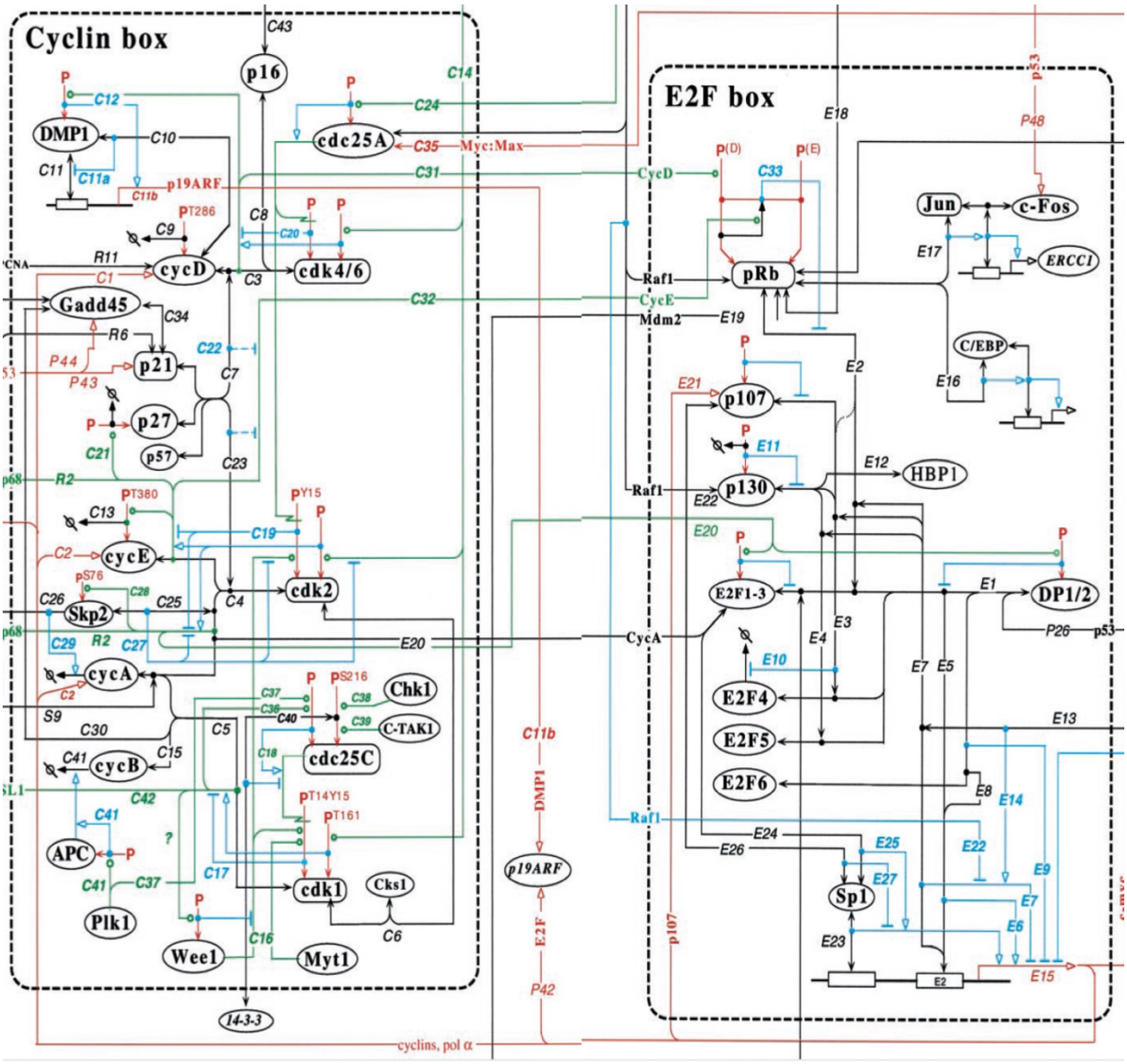

Figure 33.8. Part of a molecular interaction map of the control of the cell division cycle as understood in 1999 (Kohn, 1999). See explanations in the text. The individual steps in the map are annotated in the paper (Kohn, 1999). (Symbol definitions are listed in Figure 33.7.)

To begin with, there is more to be said about Cyclin-Cdk dimers, how they are affected by p21cip1 and how they affect pRb. Moreover, each of the aforementioned molecules have several relatives, some of which we will distinguish in our description of the control of the cell cycle via pRb and its relatives. The actions of some of these were already shown in an earlier molecular interaction map (Figure 33.8) (Kohn, 1999).

There are several types of cyclins, of which we will be concerned mainly with cyclin D and cyclin E. (Cyclin D has three types which function similarly and need not be distinguished here.) Of the several types of Cdk's, the ones that come into play are cdk4 and cdk6, which combine similarly with cyclin D, function similarly, and need not be distinguished here -- and cdk2, which combines with cyclin E. p21cip1 has an important relative, p27kip1. There are several E2F species, which we need not distinguish. Finally, pRb has important relatives, p107 and p130. You can spot all of them in Figure 33.8.

We move next to the more current picture of how the cell division control system works – the system that controls a cell's commitment to start DNA replication. This is a key decision point, fraught with danger if the genome that is to be replicated is damaged, as it often is in cancer cells, especially after chemotherapy. The decision is made at a so-called cell cycle checkpoint – specifically, the G1/S checkpoint when cells that are in cycle are confronted with the critical decision of whether to start DNA synthesis. The retinoblastoma protein, pRb, plays a central role in this decision.

Most cells in the common slow-growing tumors, by the way, are not in cycle: they are dormant in a so-called G0 state. Such cells can be activated by growth factors to move into a G1 state in the cell cycle and, after passing the G1/S checkpoint, to move toward cell division. To begin on the path to cell division, cancer cells must traverse this checkpoint, also called the restriction point, that holds up the cells' ability to begin DNA replication. The decision to traverse the G1/S checkpoint is governed by a complicated pRb-dependent molecular interaction network that is still not completely understood (Baker et al., 2022; Matthews et al., 2022). An early version of the details was assembled in the molecular interaction map with annotations for all the steps in that complicated map (Kohn, 1999). But I now show the essentials in a more up-to-date map in Figure 33.9. that should be easier to follow than a full map would be. I'll describe the essentials starting from the bottom of the map, *i.e.,* from the final outcome: the beginning of DNA synthesis with transcription of the necessary genes, one of which is dihydrofolate reductase (DHFR) (Chapter 5).

Transcription of these genes is initiated by transcription factors E2F, of which there are several and which operate as dimer complexes with DP1 or 2, as shown in the earlier more detailed map in Figure 33.8. E2F1, 2, and 3 can bind pRb and are thereby dislodged from the E2 promoter sequences; thus pRb (as well as its relatives p107 and p130) inhibit the onset of DNA replication. (There is some uncertainty about the functions of E2F4 and 5. (Baker et al., 2022; Matthews et al., 2022).)

For DNA synthesis to begin, pRb (as well as its relatives) have to be inhibited. This happens by a sequence of two regulated steps, the first regulated by cyclin D and the second by cyclin E. The steps are successive phosphorylations of pRb, which is inactivated only when fully phosphorylated through the successive actions by cyclin D-cdk4 and cyclin E-cdk2 (or their respective relatives).

(To present the effects of the sequence of pRb phosphorylations on the map, I took some liberties with the notation and recognize that a strict interpretation of the inhibition step marked in red would be ambiguous. But hopefully the description in the text will be clear.)

As pRb begins to be inhibited, transcription can begin. Interestingly, positive feedback loops come into play – in fact, two of them – because, among the transcription products from the E2 promoters, there are two critical components of the system itself: E2F and cyclin E (Figure 33.9). The effect of these positive feedbacks would be to make pRb inhibition and transcription activation of DNA synthesis genes relatively sudden, as if turning on a switch.

Next, I'll describe the two pRb phosphorylation processes, the first governed by cyclin D and coming from replication signals, the second governed by cyclin E and inhibited by DNA damage. Each process is governed by a series of molecular events that I will continue to describe in turn from the bottom towards the top (Figure 33.9).

The first set of pRb phosphorylations (P^D) is carried out by cdk4 when it is activated by binding to cyclin D. The cdk4-cyclin D dimer is stabilized by binding p27kip1 but is separated when cdk4 binds p16ink4, which prevents cdk4 from binding cyclin D. Thus, p16ink4 is an effective cdk4 inhibitor. Cyclin D is produced by transcription in response to replication signals by way of RAS, MYC, or estrogen receptor pathways.

In response to DNA damage, p16ink4 is transcribed from a gene that also produces a protein called ARF (for alternative reading frame protein) that in turn inhibits Mdm2, which inhibits p53 and blocks cell cycle entry (Chapter 32) (Matthews et al., 2022). These steps were omitted for clarity in Figure 33.9.

p27kip1 binds cyclin D-cdk4 (or cyclin D-cdk6 in different cell types) and increases cdk4 or cdk6 activity, apparently by stabilizing the complexes (Baker et al., 2022). p27kip1 binds and stabilizes these complexes thereby increasing their cyclin-dependent kinase (cdk) activities. These cdk complexes then phosphorylate the pRb protein (as well as the pRb-relatives p107 and p130) as a first step in the inactivation of these proteins.

The second set of pRb phosphorylations (P^E) is carried out by cdk2 when it is activated by binding cyclin E. The pathway is in large part similar to the cdk4-cyclin D path. The cdk2-cyclin E dimer too may be stabilized by binding p27kip1 and is inhibited when it binds p21cip1. The latter is produced when its transcription is activated by p53, which in turn is activated by being phosphorylated by ATM, which in turn is activated in response to DNA damage. The story of how ATM is activated is told in Chapter 29, including the role of the MRN complex (not shown in Figure 33.9).

The fully phosphorylated pRb can no longer bind E2F (red inhibitory step in Figure 33.9). E2F then is free to activate transcription of genes required for DNA synthesis and to initiate progress toward cell division.

The above description of the molecular interaction map in Figure 33.9 started from the final outcome, the synthesis of genes that propel the cell into S-phase and proceeded upward according to successive regulatory steps. The advantage of this type of display, which we called hierarchical, was presented in (Kohn et al., 2009), which also discussed some additional aspects of the network that were omitted for clarity in Figure 33.9. We see that, up to the level of cdk4 or cdk2, the net action is to stimulate DNA synthesis. The steps above this level show the response to DNA damage that inhibit the events below them.

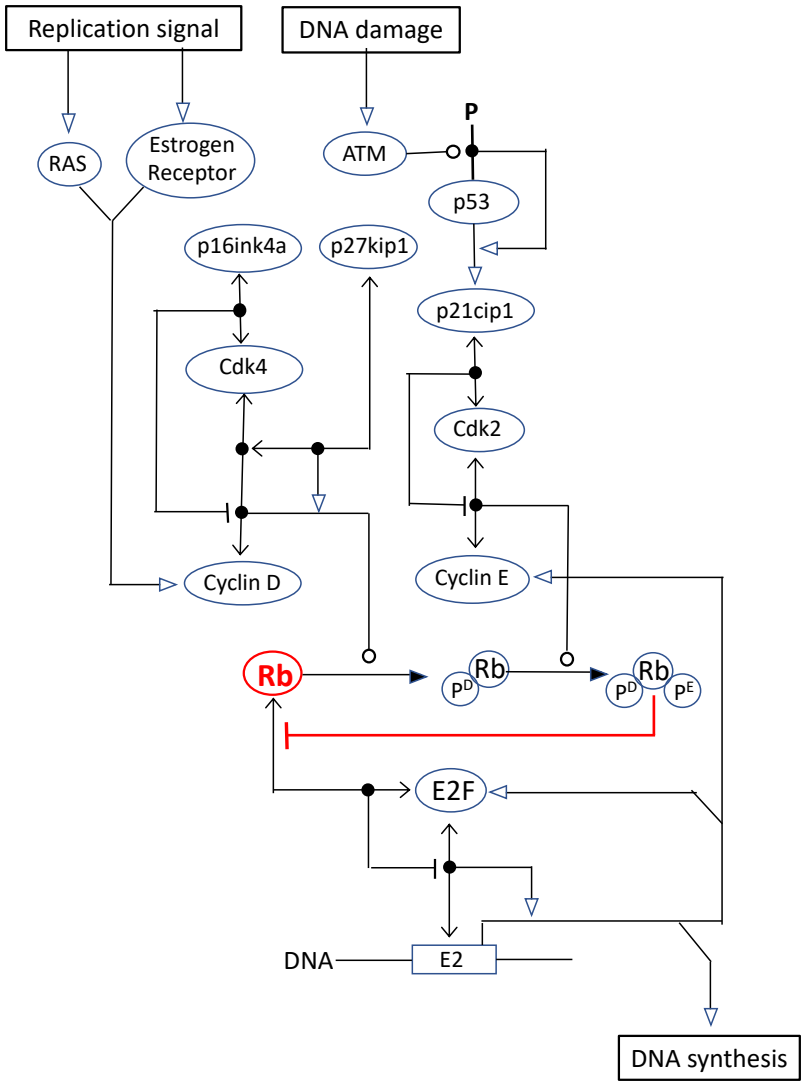

Figure 33.9. A molecular interaction map showing the hierarchy of steps leading to onset of DNA synthesis (S-phase) from responses to replication signals or DNA damage (discussed in the text above.).

The cdk4 inhibitor story.

As we saw in Figure 33.9, entry into S-phase of the cell division cycle is tightly controlled by the pRb protein, whose block of cell cycle progression can be relived by the action, first by cdk4 or cdk6 and then by cdk2. Only then can a normal cell set off on the way to dividing. In order to progress, the cell also needs cyclin D, which cdk4 needs to function. But cyclin D will only appear if its production is stimulated by replication signals coming by way of pathways from growth factors, such as RAS, MYC, or estrogen receptor. Cancer cells often have weakened pRb control and tend to enter S-phase inappropriately. Thinking that the weakness may reside at the level of cdk4 or cdk6, medicinal chemists began an intensive search for specific inhibitors of those kinases (Goel et al., 2022).

The first cdk inhibitor had actually been discovered earlier in the NCI's cancer drug screen. The drug, flavopiridol (also known as alvocidib), was active against acute myeloid leukemia in some patients (Chapter 20). But toxicity was deemed high relative to benefit and the drug was dropped from clinical trial. It turned out that the drug acted largely on cdk9, which acts on RNA during transcription – which overwhelmed its actions on cdk4/6. The search was on, therefore, for drugs that inhibit only cdk4 and cdk6.

The problem was difficult and success was far from assured. Nevertheless, and quite remarkably, by 2004, medicinal chemists had succeeded in synthesizing a highly specific cdk4/6 inhibitor that arrested tumor cells prior to S-phase accompanied by reduced pRb phosphorylation (Fry et al., 2004). By 2015, the drug, palbociclib, received accelerated FDA approval for treatment of hormone receptor positive, HER2-negative breast cancer. (HER2 is a human epidermal growth factor receptor; see Chapter 17.) Palbociclib, as well as two related drugs, abemacicilib and ribociclib, entered the mainstream of clinical practice and were considered one of the most significant advances in breast cancer treatment over the past two decades (Goel et al., 2022) (Figure 33.10).

Recent findings however suggest that exactly how the cdk4 inhibitors work may be more complicated than might have been supposed (Baker et al., 2022).

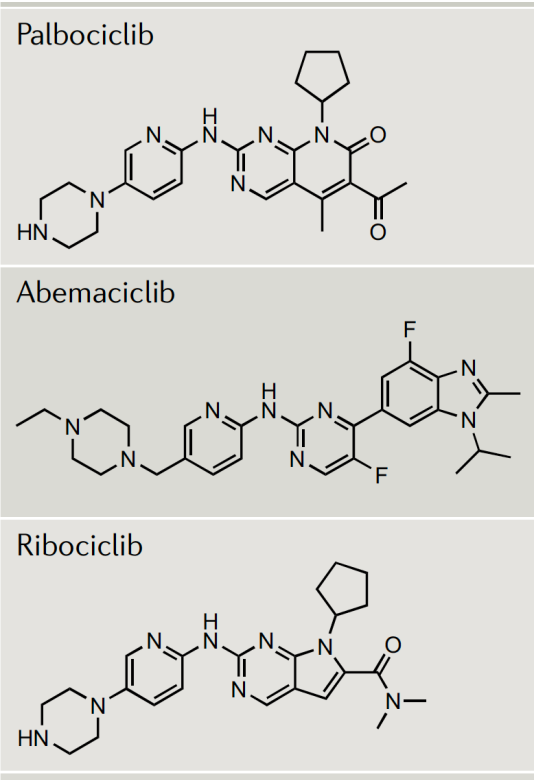

Figure 33.10. Cdk4/Cdk6 inhibitors approved for treatment of HR^+, $HER2^-$ advanced breast cancer (from (Goel et al., 2022)).

Summary

The retinoblastoma story dates back to pre-anesthesia times when the eyes having malignant tumors in them were removed from very young children but nevertheless failed to save their lives. The outlook improved after the invention of the ophthalmoscope, which allowed removal of the eye before the tumor spread. Therapy improved gradually to a current 90% cure rate of early cases by administration of chemotherapy drugs through an artery to localize chemotherapy drug to the eye. The tumor, retinoblastoma, developed from the retina and had a genetic origin, inherited from the genome of a parent or from a mutation in a stem cell in the early embryo. The former origin usually produced tumors in both eyes, while the latter resulted in a tumor in only one eye.

Retinoblastoma was one of many inherited malignancies where a mutated gene was found to have an important role in many cancers. Most cancers were found to have a defect in the molecular pathway dominated by the protein product of the retinoblastoma gene, pRb. The pRb pathway controls the progress of the cell through the cell division cycle. A defect in that control allows cancer cells to move toward inappropriate cell division. Drugs were

developed to counter this process and were found to be effective treatment of common types of breast cancer.

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