This examination consists of four sections - histopathology, multiple choice, short answer, and an essay. When answering the questions, please pay careful attention to the number of points allotted and ANSWER ONLY IN THE SPACE PROVIDED.  

SECTION 1: HISTOPATHOLOGY CASES (28 points)

1. A 4-year-old boy presents with nausea, vomiting, and general malaise. Initially, the child was diagnosed with "flu" and sent home to recover. One week later, his mother brought him back because of persistent nausea and vomiting. An X-ray revealed a circumscribed mass on one kidney, which was biopsied and processed for cytogenetic analysis. The histopathology is shown in Figure 1 (A and B). Cytogenetic analysis demonstrated a deletion in chromosome 11p13. (6 points)

What is your diagnosis? Wilms' tumor

Drawing on the histopathological features of this mass illustrated in the figure, EXPLAIN how you arrived at this diagnosis. There are a preponderance of small blue cells that have large nuclei and very little cytoplasm. There are also abortive tubules, collections of cells that appear to be forming a lumen, which is also characteristic of Wilms' tumors.

What gene is most likely deleted? WT-1

How is the deletion in this gene related to the pathogenesis of this lesion? WT-1 is a tumor suppressor gene (TSG) that is related to renal and gonadal development. Mutations in this gene are likely to decrease the susceptibility of potential tumor cells to growth inhibitory signals and thus, along with other mutations, lead to uncontrolled cell growth.

2. A 46-year-old physician comes to your office, complaining of recurrent respiratory infections and asthma that is not responsive to treatment. He states that he smokes one pack of cigarettes a day and drinks one or two beers in the evening. His father died of a respiratory disease but he is not exactly sure of the diagnosis. A section from the biopsy of his liver is shown in Figure 2 (A and B). (6 points)

What is your diagnosis? α1-antitrypsin deficiency

On what basis did you make this diagnosis? hepatocytes in this patient's liver biopsy contain large, eosinophilic inclusions and there is some expansion around the bile duct (fig 2A, left hand side). These two changes in the liver are characteristic of α1-antitrypsin deficiency.

What is the most common molecular defect in patients with this disease? patients have a mutation in the gene for α1-antitrypsin that makes the enzyme nonfunctional.

How does this molecular change produce disease? lack of functional α1-antitrypsin means that a patient will not neutralize neutrophil elastase properly. This leads to lung damage culminating in emphysema and liver damage resulting in cirrhosis.
3. A 75-year-old former insulation sprayer has a myocardial infarction and dies soon afterwards. A careful occupational history reveals that he also worked in a jewelry factory in Rhode Island for many years and has been in poor health for about the last five years. One of his consistent complaints to his family was difficulty breathing but he avoided doctors. His physician requested permission for an autopsy. The family consents and tissues are collected from a variety of organs, one of which is shown in Figure 3 (A and B). (6 points)

Identify the tissue in this section. lung

What disease did this man have? asbestosis

EXPLAIN the basis of your diagnosis. His lung tissue contains ferrous bodies that appear as gold-en, beaded rods and some fibrosis. Although ferrous bodies may be formed in response to substances other than asbestos since they are truly deposits of iron put down by macrophages, it is likely to be asbestos in this case due to history of exposure. For what other diseases was he at risk? through his job: mesothelioma, lung cancer, pleural plaques and effusions.

4. Figure 4 (A and B) illustrates a biopsy from a lesion removed from a 64-year-old woman who presents with rectal bleeding. (4 points)

From what organ was this lesion removed? colon

Is this lesion hyperplastic, benign, or malignant? malignant

What genetic changes occur CONSISTENTLY in this tumor? homozygous loss of APC, a tumor suppressor gene; mutation of k-ras, loss of a TSG on chromosome 18, and mutation of p53, another TSG.

5. A 55-year-old man presents with a persistent productive cough. He is a sales executive who smoked 2 packs of cigarettes a day for 30 years but stopped 10 years ago. X-ray revealed a large mass in the lung. You strongly suspect that the man has lung cancer and refer him for a complete work-up. The pathology report comes back with a diagnosis of small cell lung carcinoma. Figure 5 shows the histopathology of his cancer. (6 points)

How did the pathologist distinguish histologically between small cell carcinoma of the lung and adenocarcinoma of the lung? The small cell carcinoma has small, strongly basophilic staining cells that are reminiscent of lymphocytes with a large nucleus and scant cytoplasm. Small cell carcinoma tumor cells are not arranged in glands. On the other hand, adenocarcinoma tumor cells do form glands and cells appear to have eosinophilic and granular cytoplasm.

Is this cancer responsive to treatment? Explain why or why not.

Small cell carcinoma is likely to be a rapidly growing tumor since its cells are small, which may indicate little time for cell growth between divisions. A rapidly growing tumor is more responsive to therapy than a slow-growing tumor because chemotherapy and radiation therapy both target rapidly dividing cells.

What is this man's prognosis? Explain the basis of your decision.

This man's prognosis is poor. He did not present with a paraneoplastic syndrome (such as Cushing's due to overproduction of ACTH) and thus I would think that his tumor cells are very anaplastic since they don't retain the function of the neuroendocrine cells from which it is derived.
SECTION 2: MULTIPLE CHOICE QUESTIONS (2.5 points each; total of 30 points)

✓ 1. Metastasis is a complex process that is modulated at multiple points in dissemination of the cancer. Which of the following is of particular significance in the growth of metastatic cells in tissues other than the site of origin?
   A. Activation of DNA enzymes involved in DNA repair
   B. Activation of enzymes involved in detoxification of carcinogens
   C. A decrease in apoptosis of transformed cells
   D. Increase in expression of molecules, such as VEGF → angiogenesis
   E. Decrease in expression of molecules, such as E-cadherin → important for invasion

✓ 2. Abundant evidence from nuclear disasters and therapeutic use of radiation has demonstrated that ionizing radiation is a potent carcinogen. Japanese who were exposed to radiation after the bombing of Nagasaki and Hiroshima have been most intensively studied. The first cancers to appear in survivors of the bombing were:
   A. Osteosarcoma
   B. Breast cancer
   C. Lung cancer
   D. Leukemia
   E. Rhabdomyosarcoma

✓ 3. A worker in a metal smelting clinic is referred to your occupational medicine clinic for a physical examination. In your occupational history, you learn that he has been exposed to arsenic. Of which of the following cancers is the worker at risk?
   A. Glioblastoma
   B. Skin cancer
   C. Liver cancer
   D. Osteosarcoma
   E. Mesothelioma

✓ 4. Since the 1930s, there has been a steady increase in cancers of the testes, which are radiosensitive and have a good prognosis. There is currently much controversy about whether environmental carcinogens, such as endocrine disruptors, are etiologically important in the development of this cancer. The description of the above cancer refers to a:
   A. Teratoma
   B. Teratocarcinoma
   C. Embryonal carcinoma
   D. Cryptorchidism
   E. Seminoma

✗ Your molecular epidemiology laboratory is studying the role of CDK4 in the pathogenesis of glioblastoma. The most recent results of your research indicate amplification of the CDK4 gene in a high proportion of tissue samples. What effects would amplification of CDK4 have on affected cells?
   A. Cyclin D would be unable to bind to CDK4.
   B. CDK4 would be unable to phosphorylate pRb.
   C. Phosphorylation of pRb would be continuous and unregulated.
   D. CDK4 would directly activate cyclin E transcription.
   E. P21 would be inactivated.
6. Thalidomide (under the trade name thalomid) is being marketed off label for the treatment of multiple myeloma, a cancer of plasma cells. What safeguards must a physician take when treating patients with this drug?
   A. If the patient is a male, the physician must tell him to refrain from sexual intercourse during treatment.
   B. If the patient is a female, the physician must tell her to refrain from sexual intercourse during treatment.
   C. If the patient is a male, the physician must tell him that he should not have children after treatment.
   D. If the patient is female, the physician must tell her that she should not have children in the future.
   E. If the patient is male, the physician must tell him that if he has a female partner, that partner should use birth control while he is being treated.
   F. If the patient is a female, the physician must tell her that she should use birth control while being treated.

7. Cytogenetic analysis of a cancer from a 50-year old patient reveals the following karyotype.

What cancer does this patient most likely have?
   A. Chronic myelogenous leukemia
   B. Burkitt’s lymphoma
   C. Hodgkin’s lymphoma
   D. Acute leukemia
   E. Non-Hodgkin’s lymphoma

What are the consequences of this chromosomal alteration?
   A. The myc oncogene has a deletion that confers enhanced tyrosine kinase activity.
   B. The myc oncogene has a deletion that confers enhanced transcriptional activity.
   C. The myc oncogene is translocated that confers enhanced transcriptional activity.
   D. The abl oncogene has a deletion that confers enhanced tyrosine kinase activity.
   E. The abl oncogene has a deletion that confers enhanced transcriptional activity.
   F. The abl oncogene is translocated that confers enhanced tyrosine kinase activity.
8. Sun screen is widely used in the United States to protect against squamous cell carcinoma of the skin, basal cell carcinoma of the skin, and melanoma. Yet, the incidence of melanoma continues to rise. What is ONE POSSIBLE reason for this trend?

A. Melanoma may be produced by UV-A radiation and sunscreen may not protect against the complete range of this type of electromagnetic radiation.
B. Melanoma may be produced by UV-B radiation and sunscreen may not protect against the complete range of this type of radiation.
C. Melanoma may be produced by UV-C radiation and sunscreen may not protect against the complete range of this type of radiation.
D. Melanoma may be produced by X-rays and sunscreen may not protect against the complete range of this type of radiation.
E. Melanoma may be produced by visible light and sunscreen may not protect against the complete range of this type of radiation.

What type of mutation is typically produced in DNA in the skin by sun exposure?

A. T=T dimers
B. A=T dimers
C. G=G dimers
D. Single base mutations
E. Double-stranded breaks in DNA
F. Frameshift mutations

A 60 year old woman comes to your office complaining of back pain and abnormal bleeding. After a careful examination, you determine that she has a leiomyoma (also known as fibroids). What would you tell this woman about her tumor?

A. She has a benign tumor of skeletal muscle.
B. She has a malignant tumor of skeletal muscle.
C. She has a benign tumor of smooth muscle.
D. She has a malignant tumor of smooth muscle.
E. She has a benign tumor of endometrial tissue.
F. She has a malignant tumor of endometrial tissue.

What oncogene is a childhood tumor in which an activated oncogene is related to prognosis. What oncogene has been most intensively studied in this tumor?

A. C-myc
B. L-myc
C. N-myc
D. H-ras
E. N-ras
SECTION 3: SHORT ANSWERS (27 points)

1. A 50-year-old man is brought to the emergency room after an accident in the nuclear power plant where he worked. You determine that the man was exposed to approximately 8 Gy of whole body radiation and, therefore, is at high risk from acute radiation syndrome. (4 points)

What organ system is most likely to be affected by this dose of radiation? GI tract

What is the primary target cell for the radiation? endothelial cells

How does radiation exert its tissue damaging effects? Exposure of endothelial cells to radiation activates a p53-independent apoptotic pathway that involves the cleavage of sphingomyelin into ceramide by ASMase and ceramide then triggers apoptosis. Death of endothelial cells in the GI tract deprives the epithelial cells of their blood supply and thus leads to ischemia and necrosis of the gut wall. Death of these GI endothelial cells is reflected in the characteristic hemorrhage seen in patients with gastrointestinal radiation syndrome.

2. There are a variety of explanations proposed for the differences in cancer mortality rates among racial groups. Mortality from cervical cancer, for example, is 2.7 for “Whites,” 5.9 for “Blacks/African Americans”, 2.9 for “Asian American and Pacific Islanders”, 2.9 for “American Indian and Alaska Natives”, and 3.7% for “Hispanic/Latinos”.

What is the MOST LIKELY explanation (for which there is good evidence) for these disparities? (2 points)

Women who are identified as minorities have lower incidences of breast cancer compared to white women. However, this statistic may have lead to the under-diagnosis of breast cancer in minorities, which contributes to a higher mortality rate as cancers may be caught later at which point the prognosis is not as good.

3. Ataxia telangiectasia is a rare disorder, which carries a 100-fold increase risk of cancer. (3 points)

What type of protein does ATM code for? DNA repair (recombination repair, in specific)

kinase that senses DNA damage

How do mutations in the ATM gene contribute to the development of cancer? Mutations in genes involved in DNA repair lead to genetic instability syndromes. This is to say that there is an increased likelihood of the accumulation of other genetic mutations in the cells of patients who cannot properly repair the damage that is consistently occurring to their genome. The development of cancer rests on the accumulation of several non-lethal mutations and this has a higher probability of occurring in someone who has a mutation in a gene like ATM.

4. A 2-year-old child of an alcoholic mother is brought to your clinic for a routine check-up.

You note that the child has a thin upper lip and a short, upturned nose. What behavioral and developmental effects might you expect in this child? (3 points)

Behavioral: hyperactivity, irritability

Developmental: mental retardation.
5. The toxicity of chemicals is highly variable and often difficult to assess precisely. The classic measure of toxicity is the LD<sub>50</sub>. Give TWO biological explanations for possible variations in the LD<sub>50</sub> for a specific toxicant in different animal species. Give ONE example of each. (4 points)

- Some toxicants are activated by enzymes in the body and if species vary in their ability to metabolize the toxicant to its active form, then the LD<sub>50</sub> will differ. Ex. Some dyes are deactivated by the liver but reactivated in the bladder of humans, but not in other species, due to the presence of urinary glucuronidase.
- Some toxicants do not have targets to interact with in some species, but do in others. Ex. Thalidomide does not cross the placenta in rats or mice, but does in humans, and in rabbits and causes birth defects such as phocomelia in the fetus, but LD<sub>50</sub>?

6. In a recent issue of the Journal of the American Medical Association, investigators provided evidence to support a cautious approach to the treatment of low-grade prostate cancers. (4 points)

What is low-grade prostate cancer?
- A low-grade prostate cancer is one that is relatively well differentiated, shows little anaplasia.

Why would a cautious approach be indicated?
- A cautious approach may be indicated if low-grade prostate cancers progressed to high-grade prostate cancers, had metastatic potential or if low-grade prostate cancers had some chance of regression (such as CINI in women). In these cases, treatment may be more harmful than beneficial and thus should be approached with caution.

7. The majority of thyroid cancers produced after the nuclear disaster at Chernobyl were papillary tumors that occurred at a young age. This surprised US scientists who initially did not believe the results. (6 points)

What is the KEY genetic mutation that has been identified in the papillary tumors produced by radiation from the Chernobyl reactor? A RET-H4 fusion gene

Why did this genetic mutation occur at Chernobyl? The radiiodine released at Chernobyl produced β particles that lead to double-strand breaks in the chromosome containing both RET and H4. Non-homologous recombination produced the RET-H4 fusion gene.

What is the molecular basis for the aggressiveness of the Chernobyl cancers?
- RET encodes a tyrosine kinase and H4 encodes a dimersized domain of unknown function. The fusion protein is thus able to constitutively activate the Ras signaling pathway, culminating in the activation of MAP kinase, without the presence of growth factors. Thus, this mutation has self-sufficiency in growth signals, which is one contributor to its aggressiveness. However, the fusion protein also activates an antiapoptotic pathway that enables tumor cells to evade programmed cell death. A second factor that also contributes to tumor aggressiveness.
SECTION 4: ESSAY

A 45-year-old woman is referred to your surgery practice after a suspicious mammographic finding. Subsequent biopsy revealed the presence of multifocal, comedoform ductal carcinoma in situ (dcis) with no discernible foci of microinvasion. The patient is quite anxious and has many questions about the biology of dcis, risk of recurrence, and treatment options. She is particularly confused by the fact that one of her friends had a mastectomy for dcis whereas another friend had a lumpectomy with radiation for an invasive cancer. She has also heard a lot about genes in the news and wants to understand how these genes relate to dcis.

Drawing on your knowledge of biology of cancer, including its molecular genetics, outline how you would go about explaining to your patient the process of development of dcis? What would you tell her about why there is so much uncertainty about risk of recurrence and the different treatment options? Assume that your patient is an intelligent human being, able to grasp, and interested in learning, the complexities of the process of carcinogenesis. (You may use the first half of the next page for your answer, if necessary --15 points)

A DCIS is a preinvasive neoplasm. Now what does that actually mean? Well, it is a cancer, it is a collection of cells that grow in an uncontrolled way compared to other tissues in the body and they will continue to grow in this way despite the fact that the stimulus that caused the uncontrolled growth is gone. These cells have a special combination of mutations in their DNA that allow for this uncontrolled growth and also allow them to escape the protective mechanism of programmed cell death that normally allows us to get rid of tumor cells. To say that this cancer is “preinvasive” means that it has the ability to leave the duct of the breast where it was formed and to enter the surrounding tissue, but it hasn’t done this yet. If that were to happen, we would call it an invasive ductal carcinoma and that would also have the potential to metastasize to other locations in the body.

So, if DCIS is an accumulation of mutations in DNA, then we can think about a progression of a normal cell to low-grade DCIS, to high-grade DCIS, and finally to invasive ductal carcinoma. Now, to be very clear, this progression may happen but it also may not and we are not very certain about how to predict whether or not progression will occur. Most of the genetic changes that give rise to the characteristics of cancer occur as a cell progresses from normal to DCIS. This is another way to say that DCIS is very similar genetically to invasive ductal carcinoma. These two entities have similar gene expression, similar risk factors, and may even co-exist together. It has been shown that anywhere between 14% and 60% of DCIS progress to invasive ductal carcinoma. But that depends on a lot of factors that we just aren’t sure about. For example, you have a low-grade DCIS and we don’t know if that is going to progress to a high-grade DCIS or not. That’s one of the reasons that treatment options vary so much—the uncertainty of the situation. Lumpectomy with radiation therapy is the general treatment for invasive ductal carcinoma and can also be performed for DCIS. Mastectomy has also been used for treating DCIS, although it’s a more invasive procedure for a lesion that may or may not become invasive ductal carcinoma than the procedure usually used for invasive ductal carcinoma.
Due to the fact that a number of DCIS lesions do progress to invasive ductal carcinoma, a lot of people believe this is a justification for treating DCIS, although we are uncertain about what would happen if we left it alone.

What about the specific genes that are noted in the profession.

Nicely organized and well-explained essay.

Miscellaneous Notes