Evolutionary Medicine

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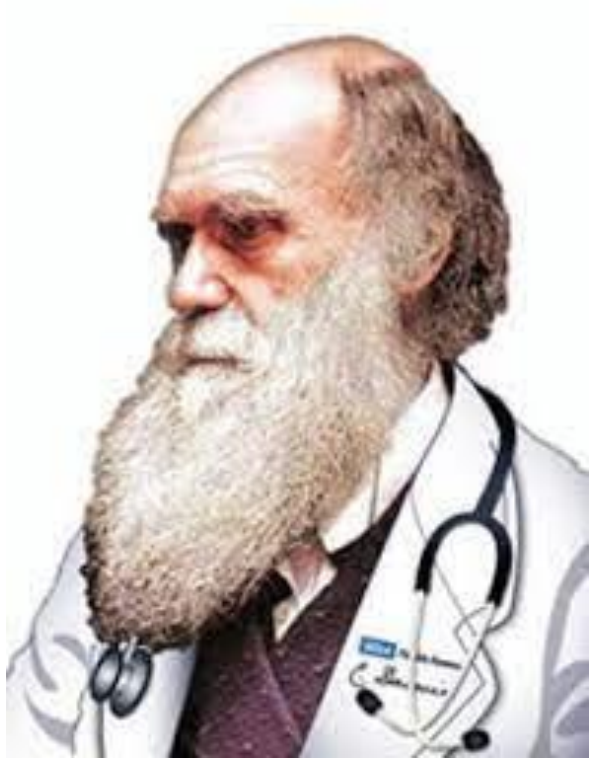

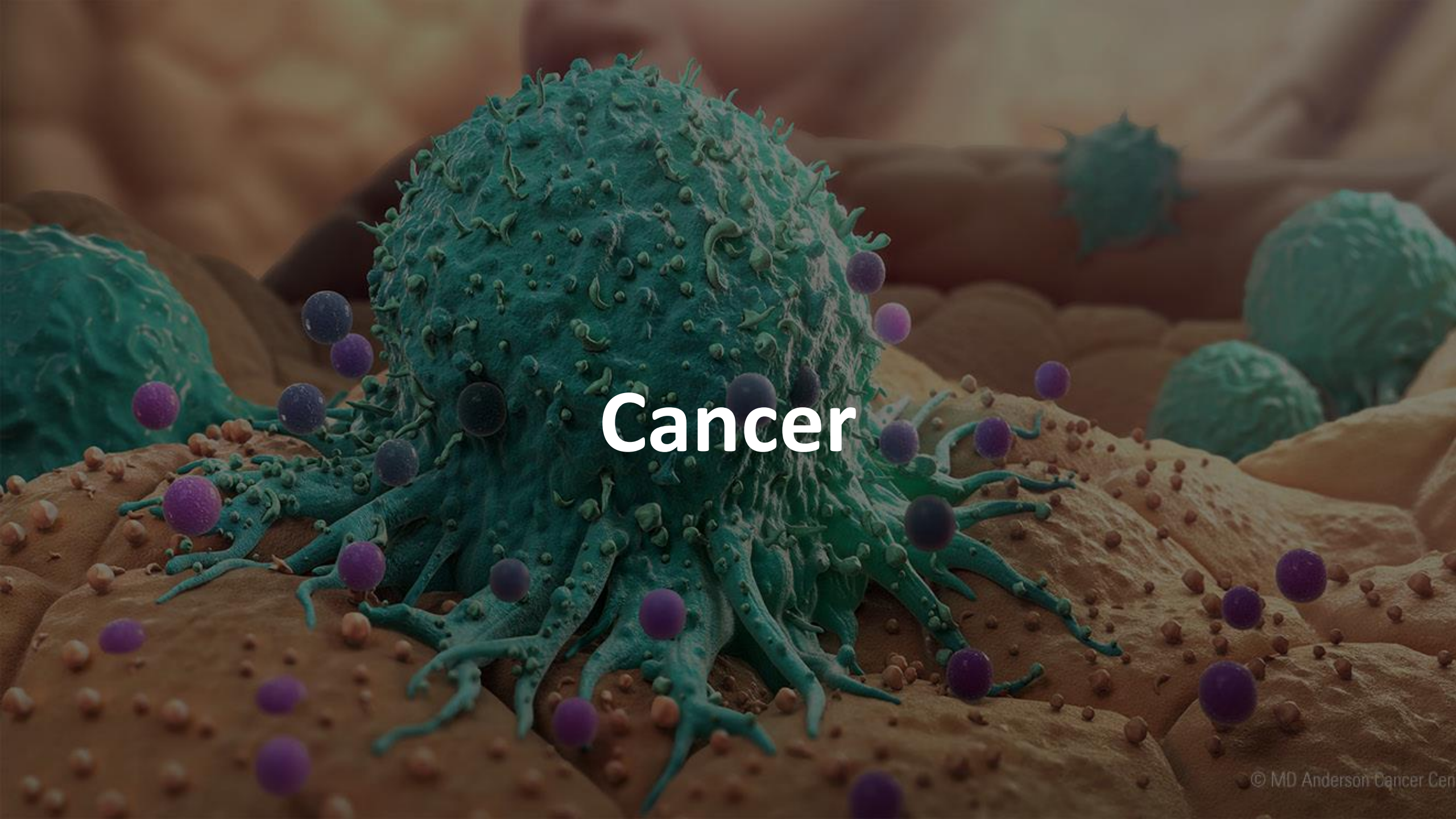
Cancer
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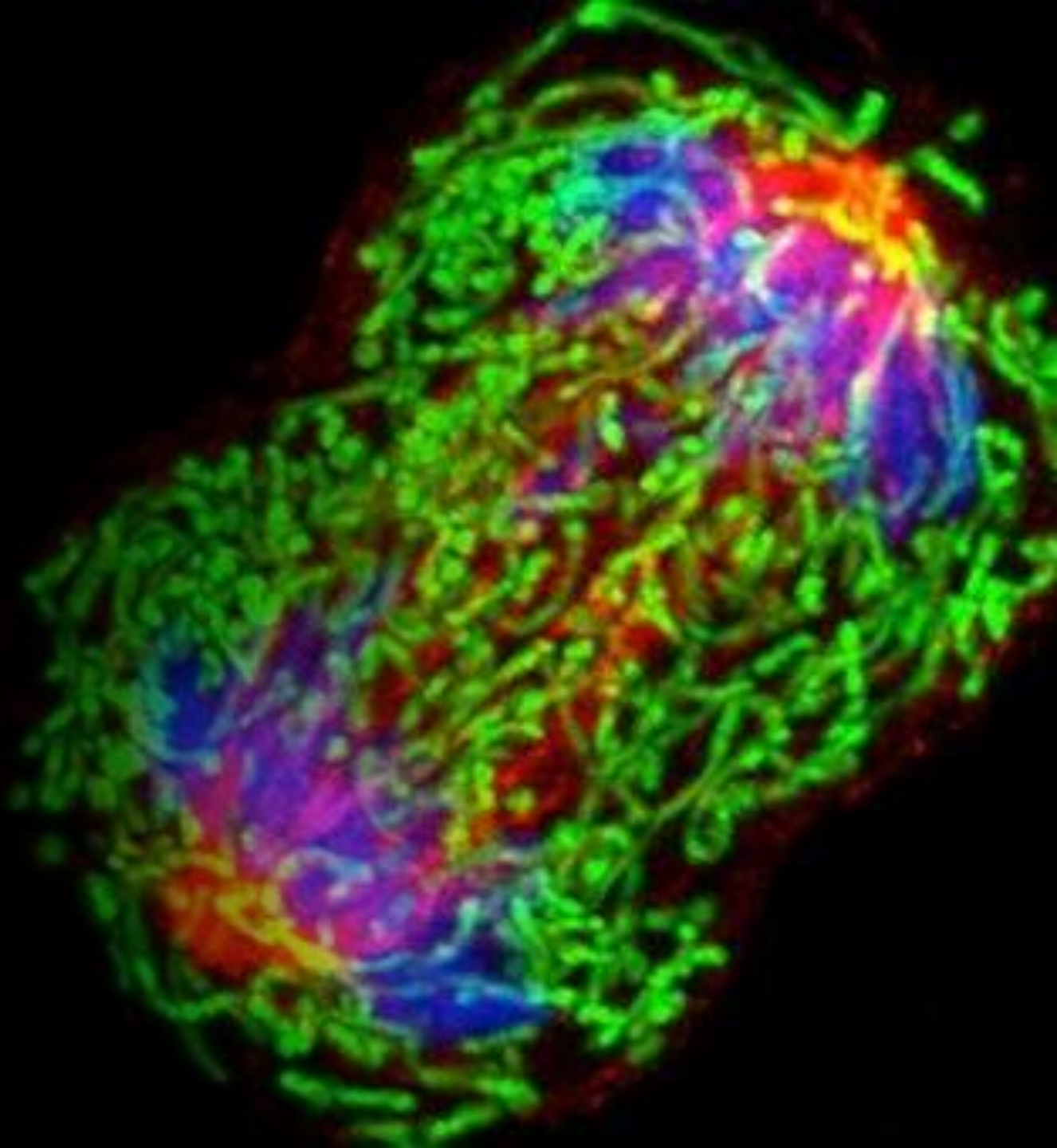
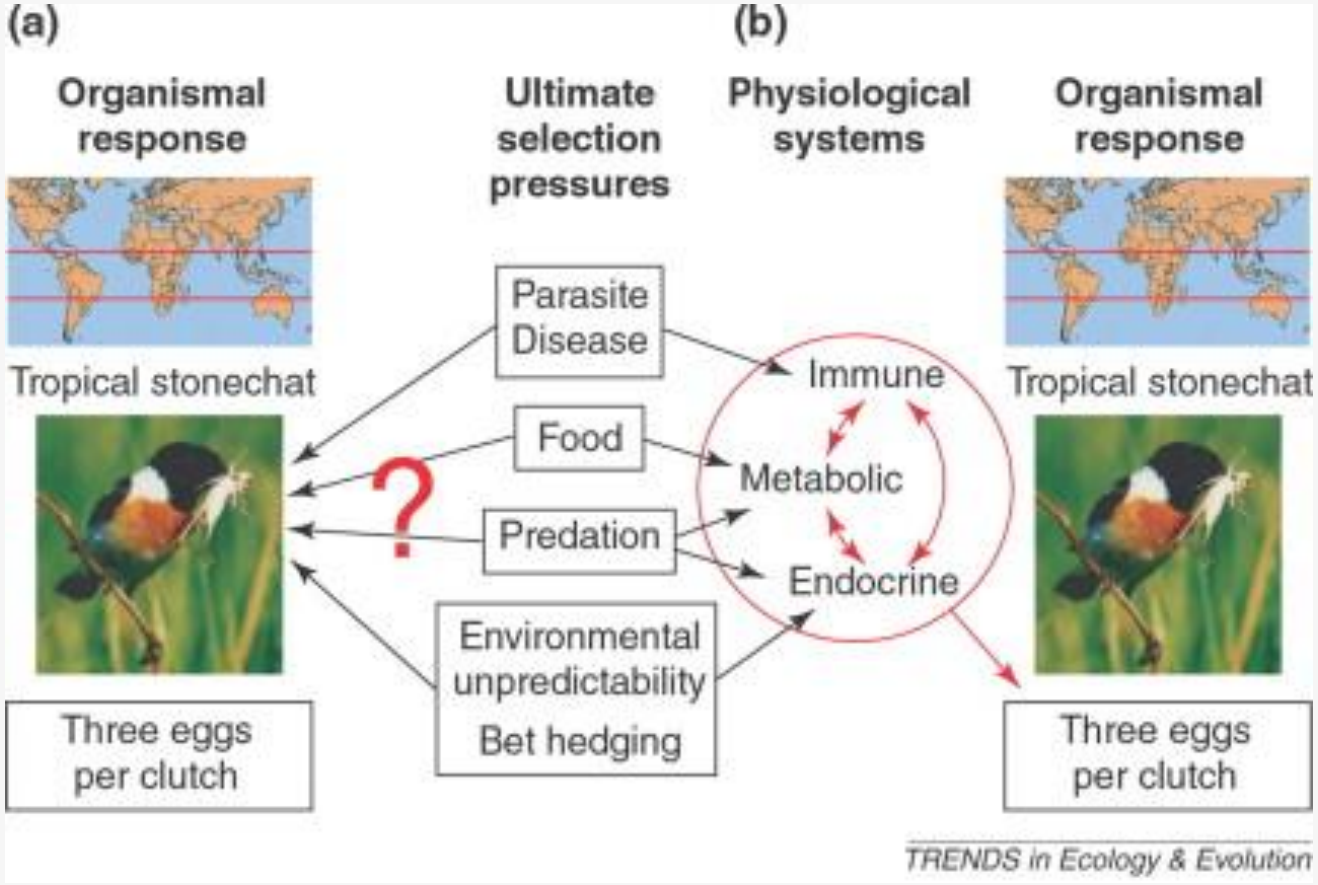
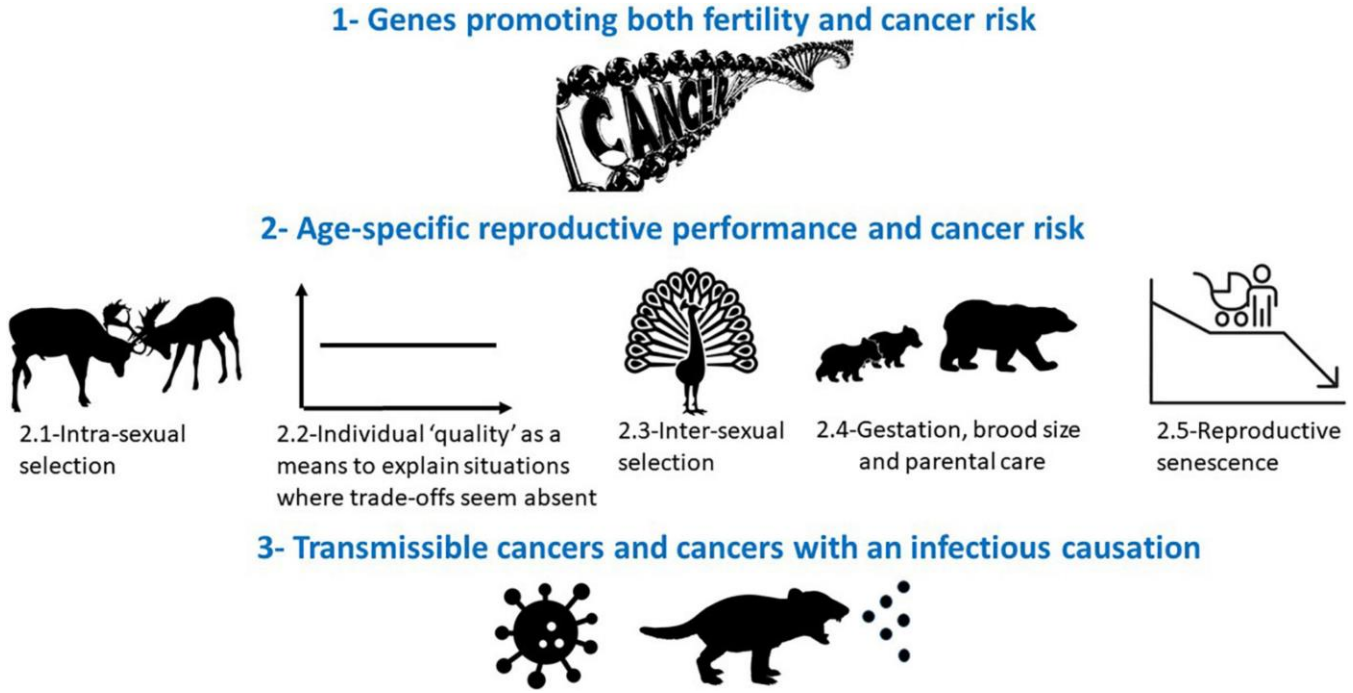
Life History and its Trade-offs

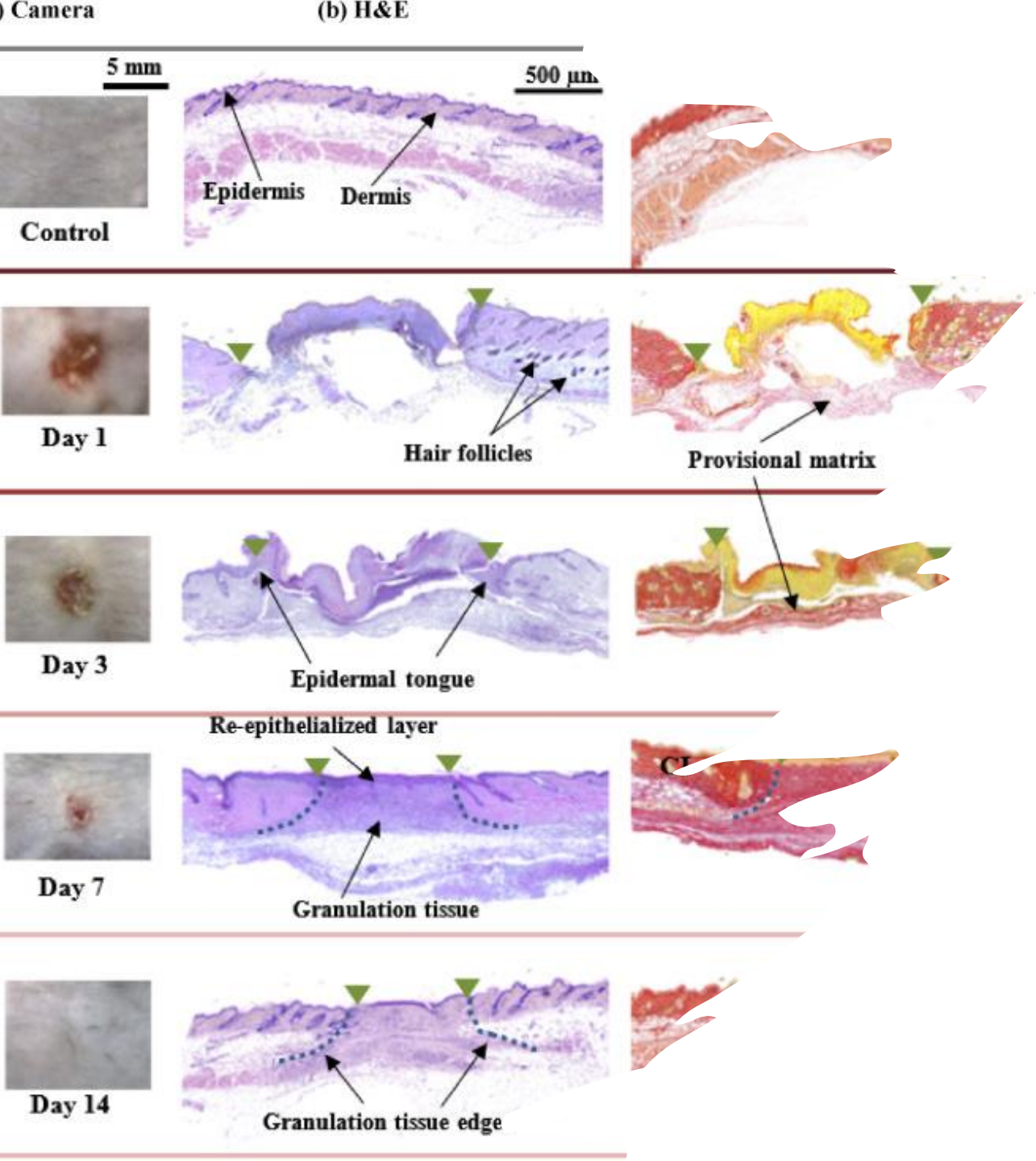




- Species have evolved their life histories to maximize reproductive success. Many of the traits underlying these life histories involve the relative allocation of resources among growth, reproduction, and maintenance. Thus, some species have evolved “fast” life histories that feature rapid growth to small body size, high reproductive effort, low levels of tissue repair, and short lifespan, whereas others have “slow” life histories with slow growth to a larger body size, lower (but likely prolonged) reproductive effort, investment in tissue repair, and a long lifespan (see Jones et al. 2014).

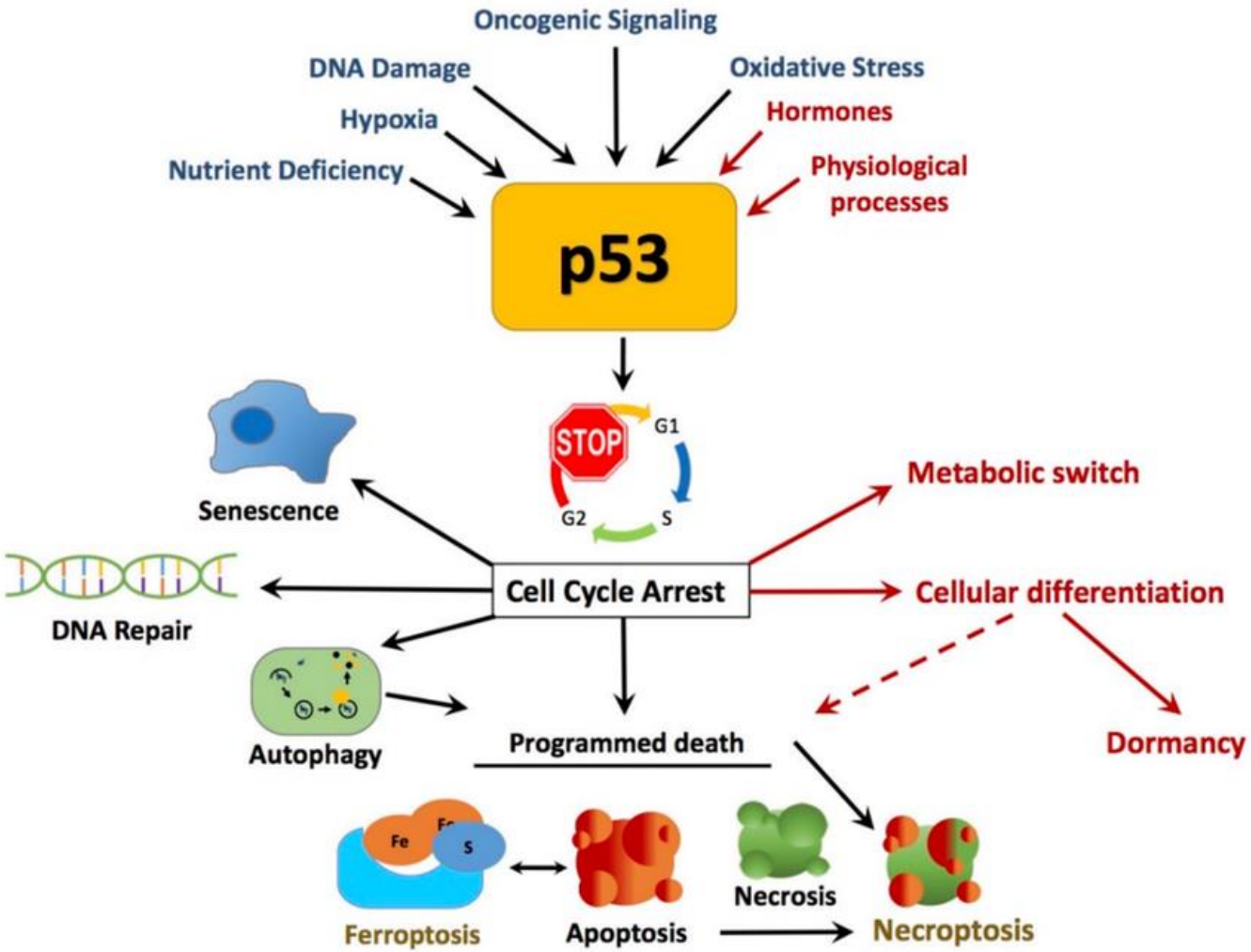
- Accordingly, species will have evolved tumor suppressor mechanisms appropriate to their “chosen” life history, in part explaining the similar rates of cancer in small and large species. With some exceptions, selection in general acts to maximize reproductive success rather than longevity, and this declining force of selection with age predicts that cancer suppression mechanisms will be relatively less effective in ageing organisms. This may explain in part the increased incidence of cancer as human longevity is increased by improved nutrition and more effective public health interventions.





- Other more specific trade- offs may occur. For example, tissue repair processes such as wound healing require a supply of stem cells able to proliferate and migrate to or within the injured site, as well as the capacity to form new blood vessels, and inflammation occurs at the site of the wound. These capacities are reminiscent of some of the hallmarks of cancer, and similar molecular mechanisms appear to be involved (see Neves et al. 2015). It may be that species that have evolved highly effective wound healing mechanisms, possibly as a result of behaviors that risk physical injury, will be more susceptible to the development of cancer. Similarly, there may be correlations between placental invasiveness and susceptibility to tumor metastasis.

- There may also be trade- offs between reproduction, ageing, and susceptibility to cancer. One molecular mechanism mediating such trade- offs involves the tumor suppressor gene *p53*, which responds to cell damage by initiating cell cycle arrest or apoptosis. We have already seen evidence that larger and long- lived animals have more copies of this gene. There is emerging evidence that *p53* also has roles in ageing (probably mediated by impaired tissue repair) and reproduction (probably mediated in mammals by effects on embryonic implantation). Although *p53* loss- of- function mutations are a major cause of human cancers, the naturally occurring *p53* polymorphisms, which seem to be the targets of selection in some human populations (Shi et al. 2009), appear to have more subtle effects; there are differences between alleles at position 72 in their relative capacities for tumor suppression (R72 allele > P72 allele) and age ingrelated functions (P72 > R72). The maternal P72 allele also appears to increase the risk of twin births in humans and, intriguingly, cancer incidence was also higher among the first- degree relatives of these mothers (Tagliani- Ribeiro et al. 2012).



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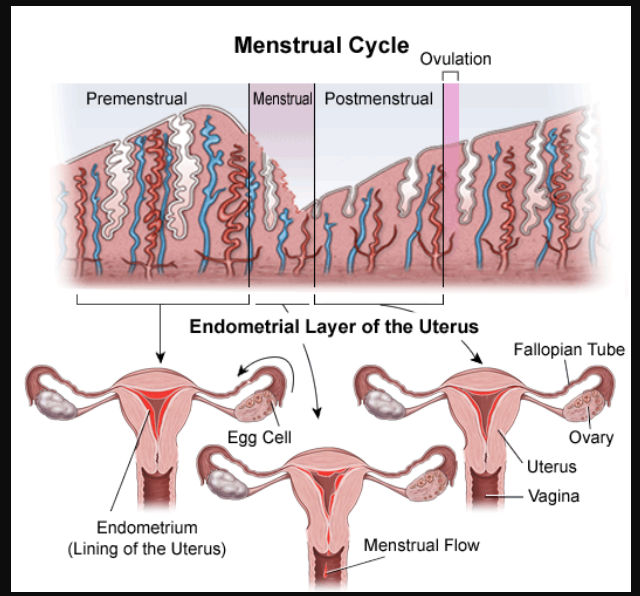
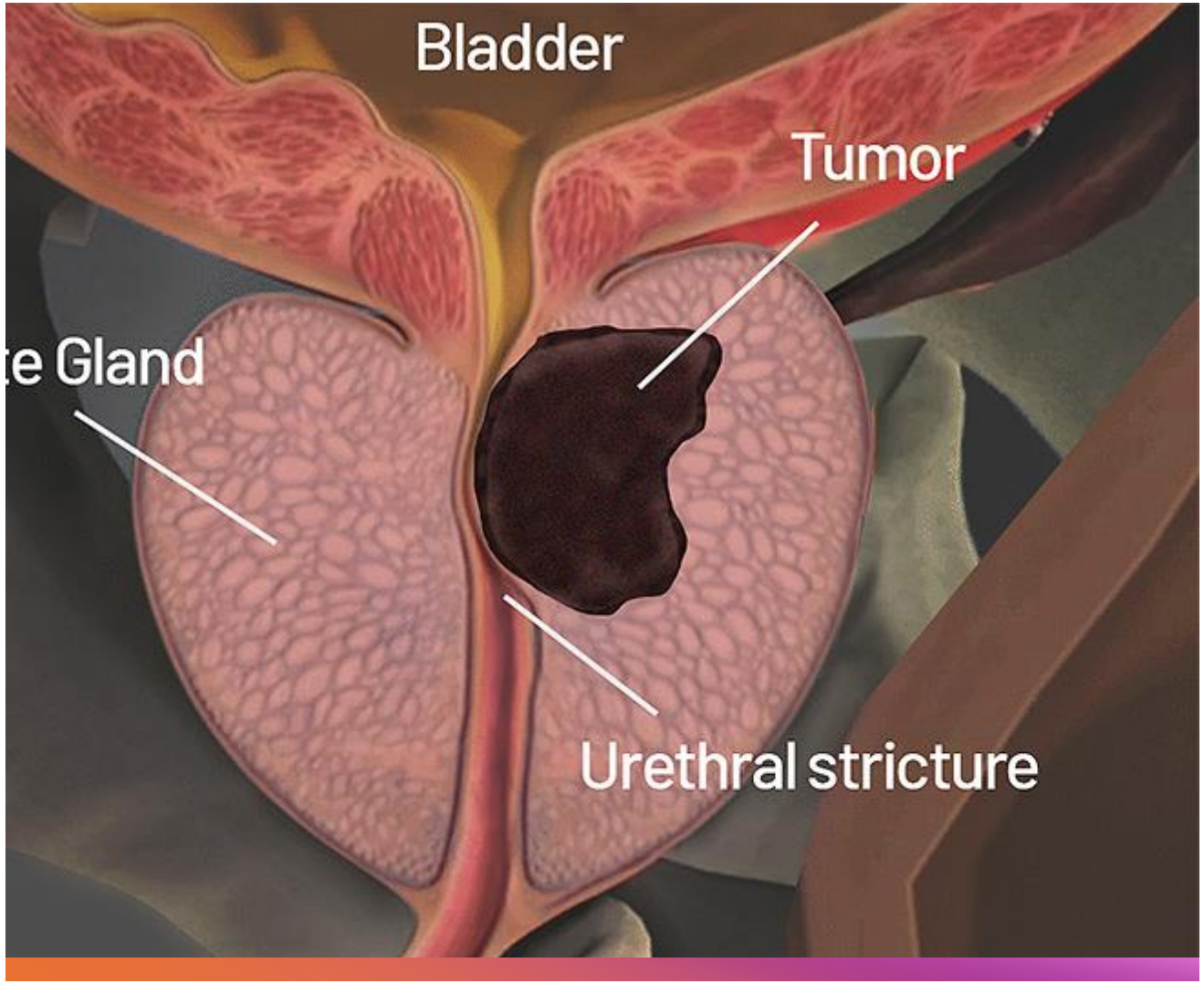
- Trade- offs between fertility and tumor suppression are examples of antagonistic pleiotropy. A similar trade- off involving the tumor suppressor gene *BRCA1*/2. Another demonstration of a relevant life- history trade- off in humans comes from the multigenerational Framingham study introduced, where the negative correlation between female reproductive success and ageing appeared to be mediated by genes linked to cancer susceptibility (see Wang et al. 2013).
- Some neoplasms are directly linked to periods of particular developmental plasticity, and this can explain the age distribution of certain cancers. For example, tumors of tissues that primarily proliferate in early life generally present as childhood tumors, such as Wilm's tumor of the kidney or rhabdomyosarcoma of muscle. Osteosarcoma, a tumor of bone, generally appears during periods of rapid peri- adolescent bone growth. In contrast, the risk of most epithelial tumors such as colon cancer increases as an individual ages because these tissues replicate through life and the risk of multiple mutations increases with age

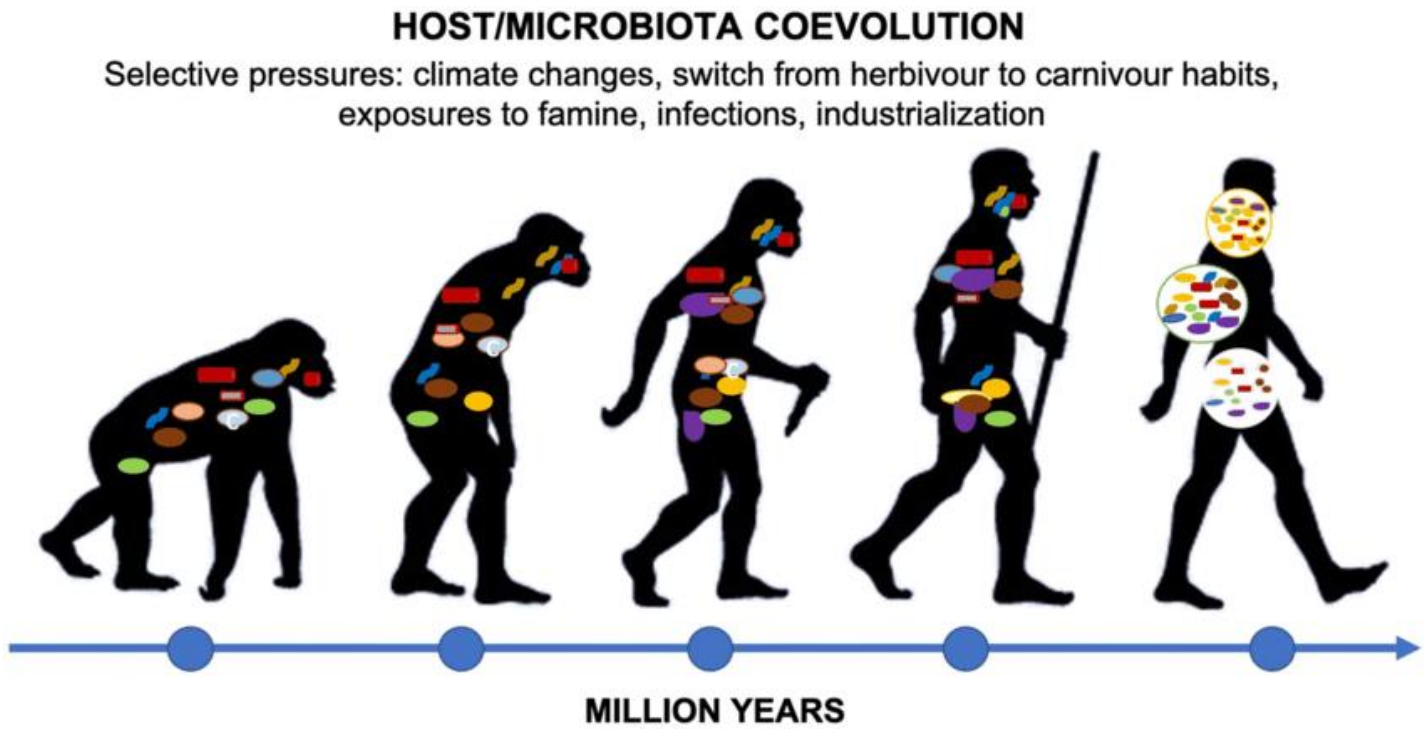
- Breast cancer, even in the absence of *BRCA* mutation, represents an example where cultural change affecting life- history phasing in the form of reproductive behavior has clearly played a role in altering the risk of disease. It has been known for centuries that celibate women are more likely to develop breast cancer (but have less cervical cancer, which is induced by infection with the human papillomavirus via intercourse). Celibate women are characterized by an uninterrupted cycle of exposure to estrogen and progesterone from menarche to menopause and by an absence of lactation. The more children a woman has, the lower her risk of developing breast cancer (see Ewertz et al. 1990). Whereas a hunter-gatherer woman might only have 100– 150 menstrual cycles during her life because of the interruptions of pregnancy and lactation, a modern Western woman may be exposed to 500 cycles. Thus the nature of the hormonal exposures is very different. The result is that the modern woman has constant proliferative stress on the ductal epithelium driven by estrogen and progesterone without any period of intervening lactation. Lactation itself leads to a loss and renewal of ductal epithelial cells, thus removing many cells with somatic mutations. In one Chinese population where women tend to feed only from the right breast, cancer is more common in the left breast, showing that exudation of epithelial cells in milk is indeed protective (see Ing et al. 1977).



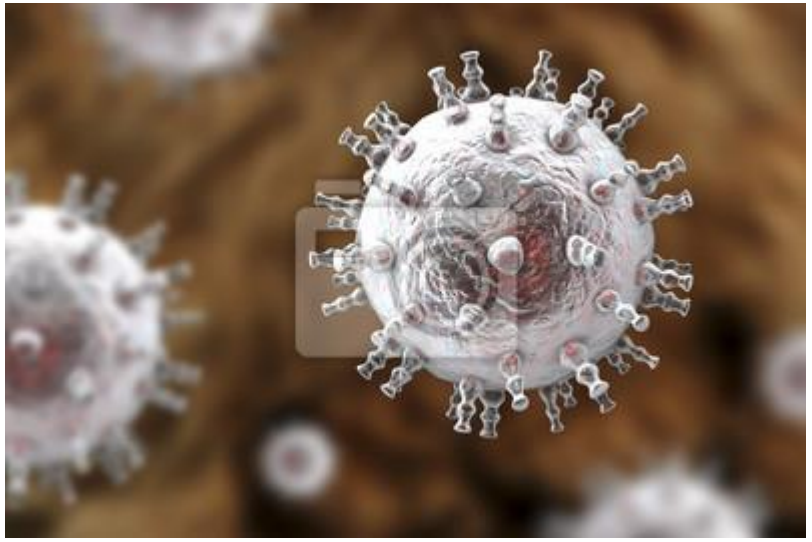
- In men, the incidence of prostate cancer increases strongly with age and shows wide geographical variation. The proliferation of this tumor is frequently testosterone dependent, and therapy involves anti-androgenic medication. There is evidence that the risk of prostate cancer is related to lifetime exposure to testosterone, and in turn testosterone levels are influenced by age, by energy intake, and (as well demonstrated in animal studies) by behavioral factors related to aggressiveness. This suggests that human populations characterized by good nutrition and/or a high level of social interaction requiring aggressive behavior should have high testosterone levels in young men and a high incidence of prostate cancer in older men. Such a relationship has been demonstrated by a study showing that testosterone levels of young men are significantly associated with population disparities in the incidence of prostate cancer in older men, providing evidence for a life-history trade-off mediated by testosterone between early reproductive effort and later health (see Alvarado 2013).



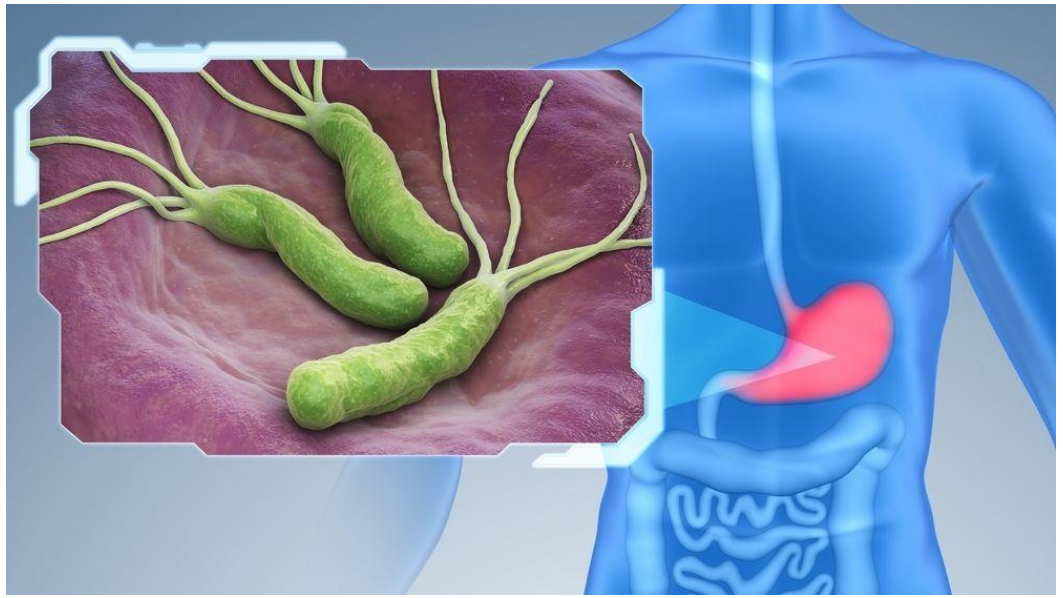
Coevolution with Microbes



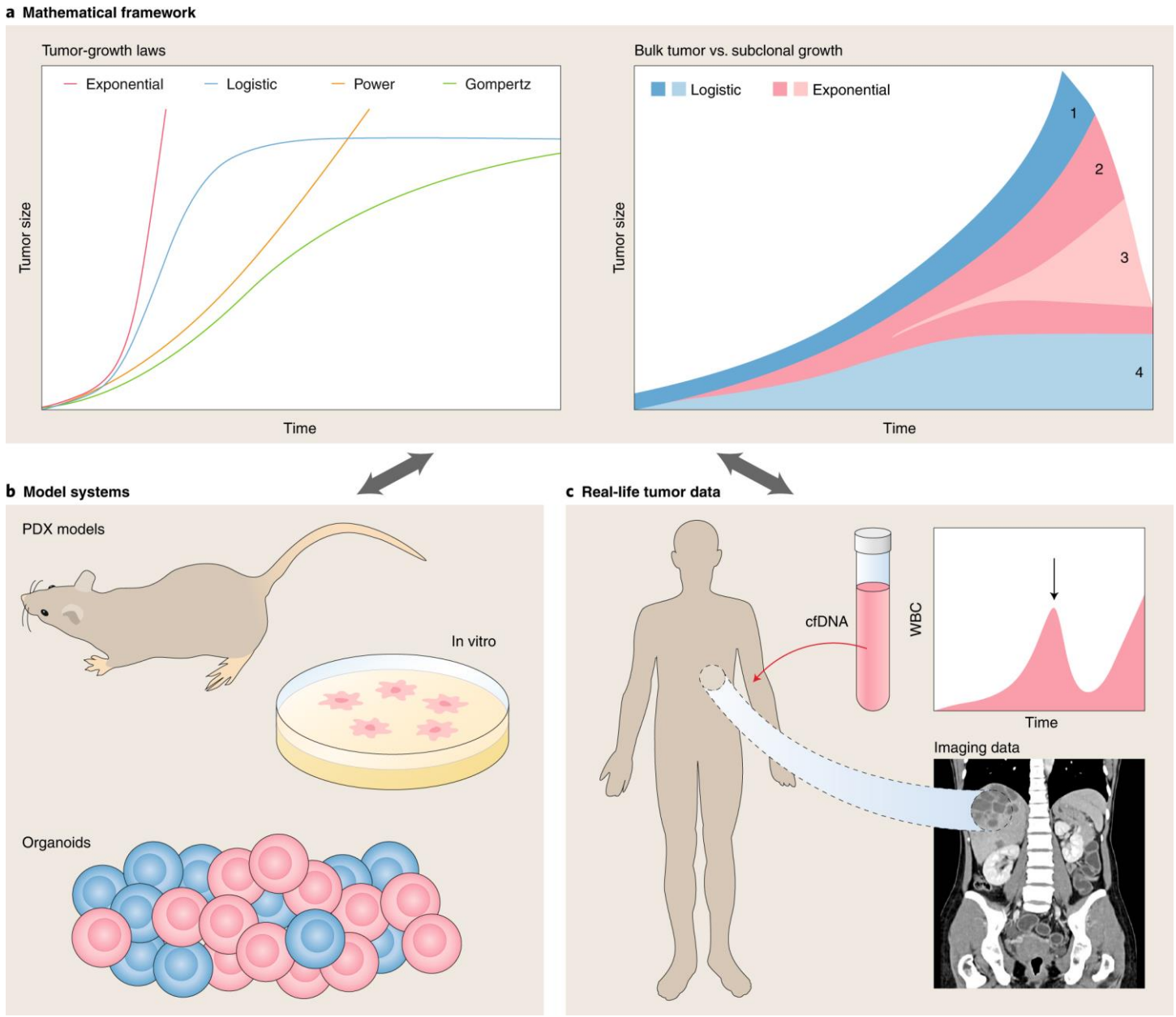
Some 15 to 20% of human cancers are thought be the result of infections. Examples of these causative organisms include viruses (e.g., herpesvirus-related Kaposi's sarcoma, hepatitis C virus and liver cancer, papillomavirus and cervical cancer), bacteria (*Helicobacter pylori* and gastric cancer), and parasites (schistosomiasis and bladder cancer). The causal nature of these organisms is clearly demonstrated by the rapid drop in incidence of their associated cancers after the introduction of vaccination or eradication programs. Why do infections lead to cancer? One explanation is that the inflammation associated with infection drives oncogenesis, for example by increasing levels of mutagens (such as reactive oxygen species produced by neutrophils) or proliferative signals (growth factors) or by increasing tissue permeability allowing tumor invasion. It is likely that cancers associated with bacterial (e.g. *Helicobacter*) and some viral (hepatitis C) infections arise in this way. But some tumor viruses act more directly on the host genome by inserting oncogenic genes that dysregulate cellular signaling systems, leading to loss of endogenous control over cell replication and proliferation. For example, human papillomavirus can integrate into the host genome, and the resulting oncogene products inactivate host tumor suppressor proteins (see Nguyen et al. 2014).
Why has evolution failed to develop mechanisms to avoid infection-related cancers? Since only a small proportion of infections with causative organisms lead to oncogenesis, we can conclude that infection is necessary but not sufficient for oncogenesis and that other host or environmental factors are required. Additionally some tumor-causing viruses, such as adenovirus, are oncogenic in some species but cause only mild infections in others. Oncogenesis mediated through the inflammatory pathway is arguably one of the costs of this defensive mechanism. Therefore, infection-related oncogenesis
can be considered as an aspect of virulence or infection-related morbidity.

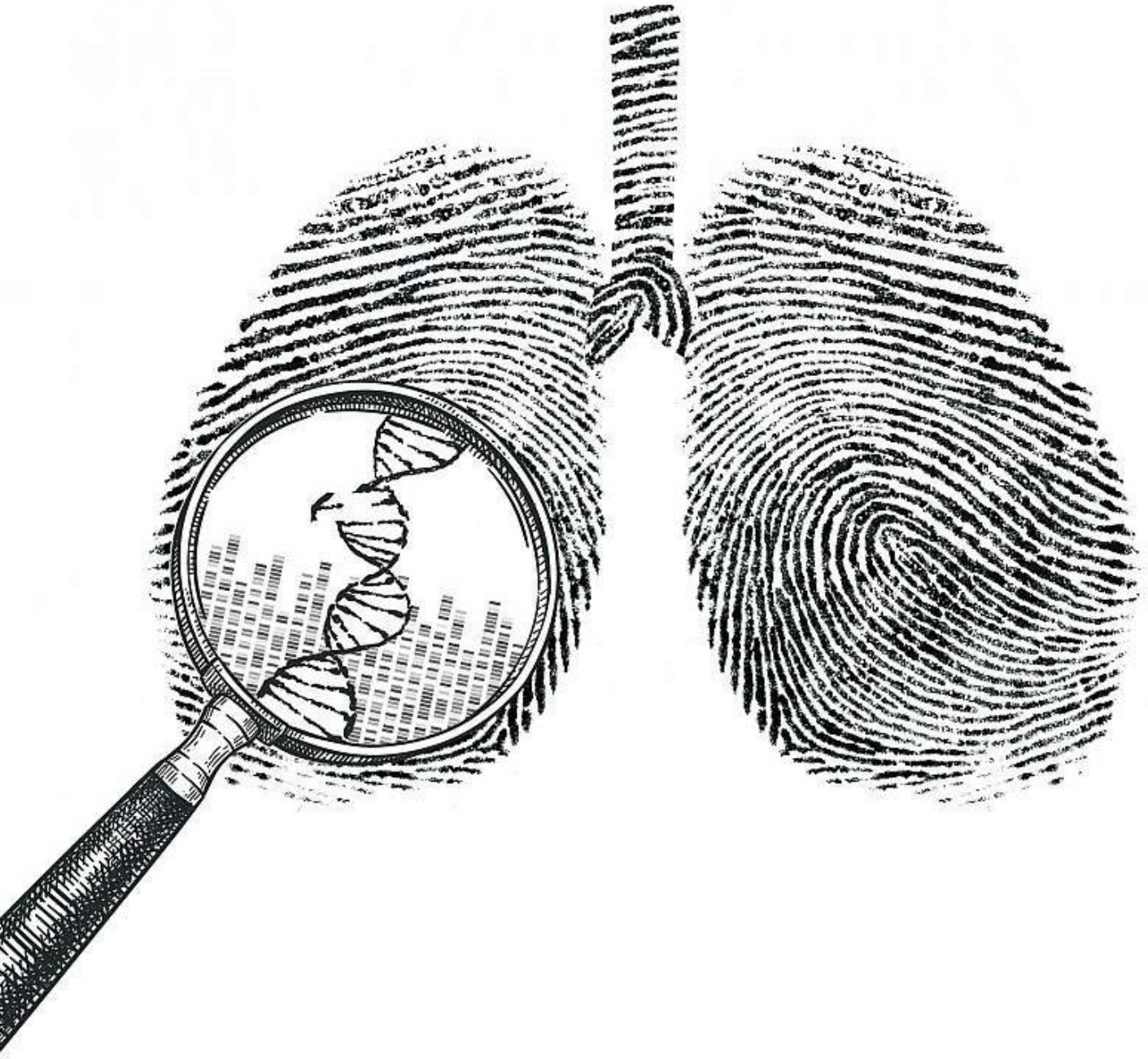


Kaposis sarcoma_herpes virus



Implications of an Evolutionary Approach for the Prevention and Treatment of Cancer

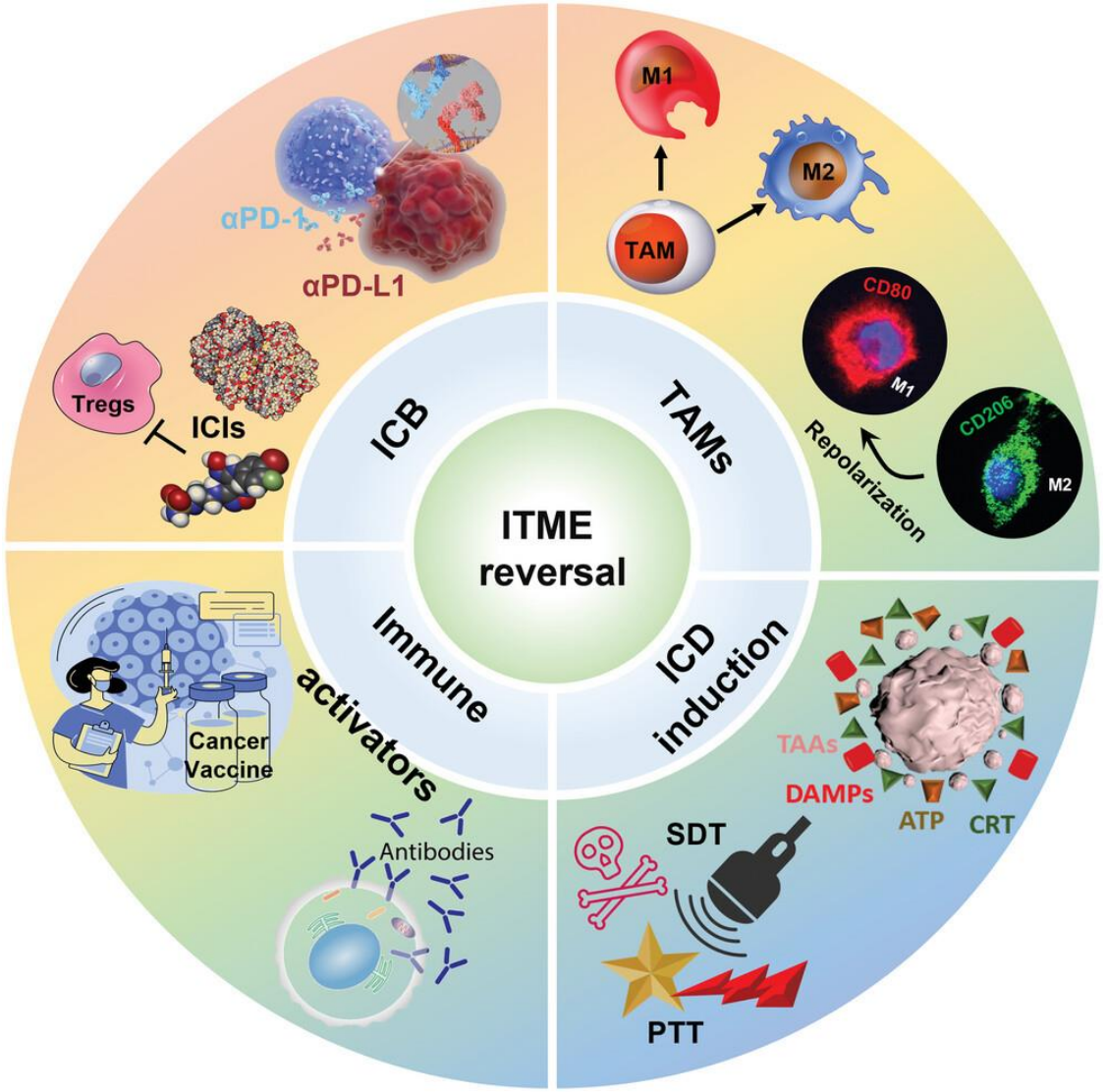




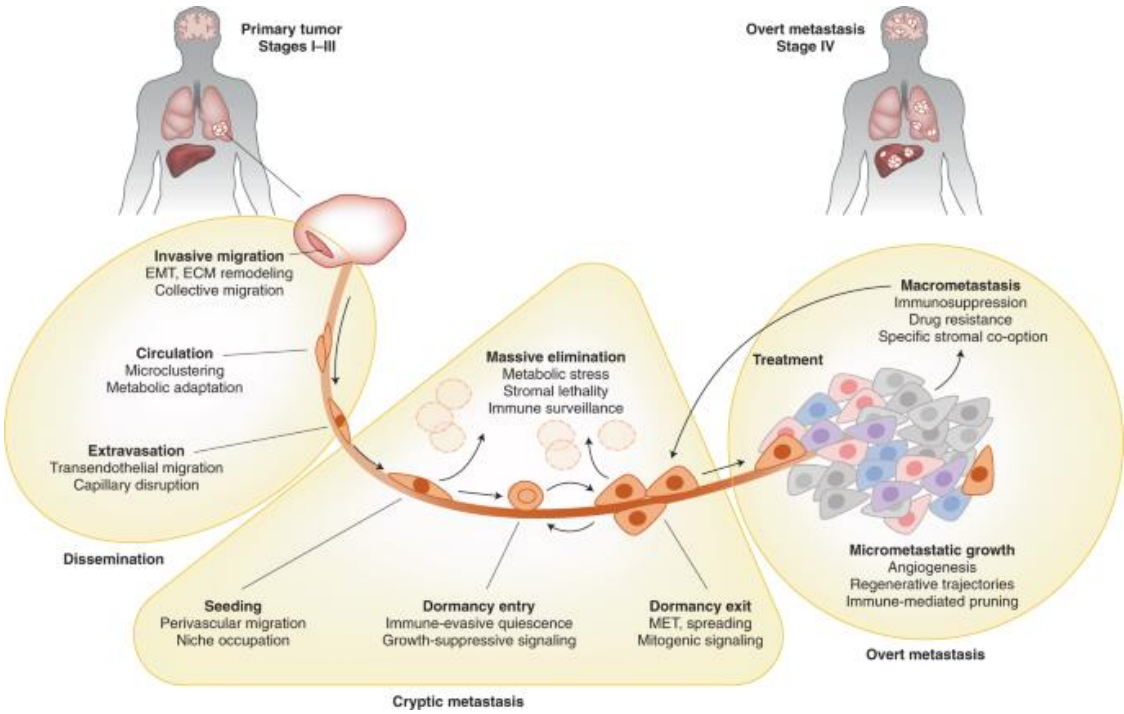
- **Prevention**
- How can evolutionary perspectives on cancer inform our approaches to prevention and treatment?
- First, appreciation of the role of environmental and life-history factors can help to prevent the development of the disease: examples include avoidance of causative environmental factors (e.g., smoking) and modification of exposure to life-history factors (e.g., use of estrogen receptor antagonists such as tamoxifen to modulate exposure to estrogen in high-risk women). An appreciation of the role of inflammation in carcinogenesis and metastasis helps us to understand the apparent protective effect of long-term use of anti-inflammatory medications such as aspirin and non-steroidal anti-inflammatory drugs (NSAIDs) against the development of colorectal cancer and possibly also breast cancer. Finally, knowledge that the efficacy of tumor suppressor mechanisms differs across species according to theirevolved life history can prompt research into new modalities to prevent malignant transformation or tumor metastasis in humans.

Treatment

- The primary treatment strategy for cancers in humans is complete or partial surgical removal of the tumor, where possible. This may be precededand or followed by systemic chemotherapy with cytotoxic drugs, or by localized radiotherapy, with the aims of reducing tumor bulk before surgery and/or killing or depleting any tumor cells remaining after surgery. Sometimes, particular aspects of the tumor cell phenotype, such as surface receptor expression, are targeted with specific agents (e.g., tamoxifen for estrogen-receptor-positive breast cancer). All these approaches are usually effective initially, although at the cost of considerable toxicity to the patient. However, in most cases the tumor recurs in a form that is resistant to the initial chemotherapy. Most tumors and their metastases are formed of multiple subpopulations of cells with different suites of mutations, and consequently different phenotypes, evolving according to the spatially and temporally differing microenvironment across the tumor. The initially predominant sub- clones can be viewed as those having the highest fitness in their environment; since resistence to chemotherapy has costs, such as diversion of metabolic effort to drug detoxification, then it is likely that these fittest sub- clones will be sensitive to therapy. However, exposure to cytotoxic chemotherapy, while killing sensitive cells, will select for a population of resistant cells that, although they may have been less dominant (i.e., had lower fitness) in the original tumor environment, will expand to fill the ecological niche left by the death of the original population of sensitive cells.



- There are several implications of this evolutionary perspective. First, tumors containing high sub- clone diversity will contain more genetic variation from which resistance to therapy can be selected. This implies that, before treatment, multiple biopsies are required to assess the phenotypes of the predominant sub- clones within a tumor in order to optimize targeted chemotherapy, since a single biopsy may only sample a fraction of the sub- clones. Indeed, the extent of genetic diversity (mutational load) within a tumor can itself be used as a prognostic indicator for the development of resistance and disease progression. Secondly, the genotypes and phenotypes of the predominant tumor clones emerging after relapse from chemotherapy will be very different from those before treatment. Understanding this can help guide subsequent rounds of treatment. Thirdly, although the goal of most current cancer treatment is to eradicate all tumor cells by using chemotherapy at the maximum dose intensity that can be tolerated, it has been suggested that this may not be the best approach to balance the course of the disease with the patient's quality of life. Modeling and experimental studies show that "adaptive therapy," which uses continuously modulated schedules of low-dose chemotherapy aiming to keep tumor size constant, results in stable disease and prolonged survival with minimal therapy-related toxicity (see Gatenby et al. 2009). Adaptive therapy aims to allow the survival of a significant number of chemosensitive cells, and these "fitter" cells will suppress the growth of the population of resistant cells by avoiding rapid proliferation of a treatment-resistant clone. The fourth point concerns the treatment approach to metastatic cancer. Metastases will contain only a proportion of the genetic diversity ofthe primary tumor, and metastasized tumor clones must adapt to the host tissue environment. There is evidence that metastases from different primary tumors adapt convergently to the environment of the new host tissue. For example, liver metastases from different primary cancer sites appear to evolve towards a common liver-adapted phenotype. These observations suggest that treatment of metastatic disease should take account of the features of the host tissue as well as of the tissue at the site of the primary tumor (see Cunningham et al. 2015)



Key Points

- Cancer is the uncontrolled growth and spread of abnormal cells. The cellular abnormalities that characterize cancer generally represent dysfunction of the evolved control mechanisms that allow cooperative multicellularity.
- Cancer typically begins as a single clone of mutated cells, but the high mutation and proliferation rates of cancer cells result in the formation of multiple sub-clones in the tumor with diverse suites of mutations that respond differently to selective pressures within the tumor microenvironment (somatic evolution).
- This heterogeneity and the high genetic variation within tumors represent a challenge for chemotherapy in particular, because treatment-resistant cells are invariably present and undergo rapid clonal expansion after sensitive cells are killed.
- The incidence of cancer appears to be increasing worldwide as populations age, although there are wide variations by tumor type, geographical area, and demography.
- Lifetime cancer risk is modulated by evolutionary mechanisms such as environmental novelty, life-history traits, and burden of infection.
- Application of these evolutionary insights may lead to new approaches to cancer prevention and treatment.

Cancer Palaeopathology

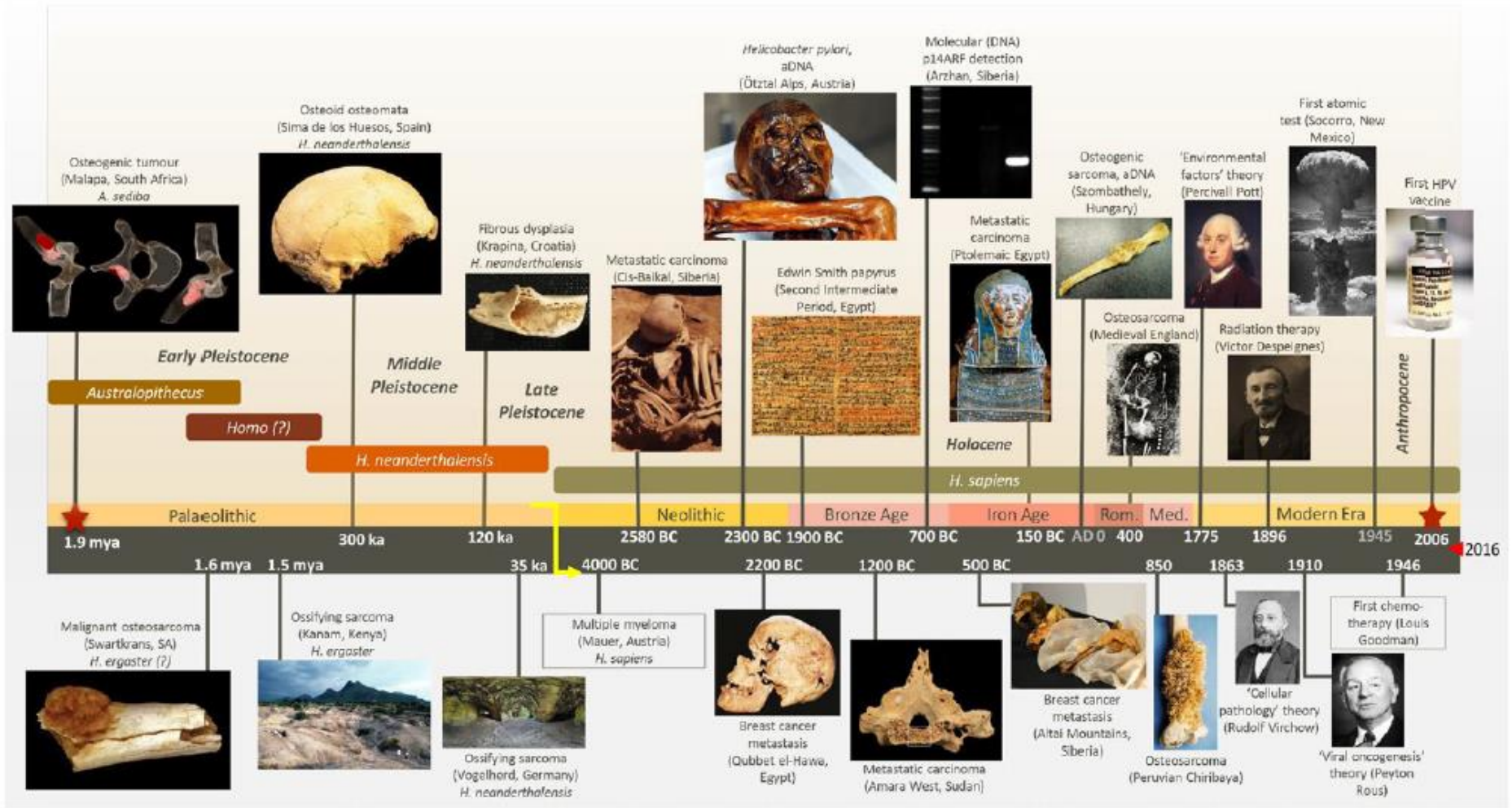


FIGURE 1 Chronological incidence of prehistoric oncogenic tumours and important milestones concerning cancer aetiology and treatment (Binder et al., 2014; Bona et al., 2014; Monge et al., 2013; Odes et al., 2016; Phelan et al., 2007; Randolph-Quinney et al., 2016) ('Rom.' and 'Med.' referes to Roman and Medieval Periods, respectively).

Thank you fo your attention!