# Pancreatic cancer pathology viewed in the light of evolution

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**Abstract**
One way to understand ductal adenocarcinoma of the pancreas (pancreatic cancer) is to view it as unimaginably large numbers of evolving living organisms interacting with their environment. This "evolutionary view" creates both expected and surprising perspectives in all stages of neoplastic progression. Advances in the field will require greater attention to this critical evolutionary prospective.

**Keywords** Pancreas cancer · Pancreatic cancer · Darwin · Evolution · Pancreatic intraepithelial neoplasia · Intraductal papillary mucinous neoplasm

## 1 Introduction

Theodosius Dobzhansky famously wrote that "nothing in the biological aspects of medicine makes sense except in the light of evolution," and yet, with the exception of elegant mathematical modeling based on evolutionary principles, much of today's discourse on pancreatic cancer fails to include an evolutionary perspective [1–4]. Here we ask if any insights can be gained by viewing the pathology and genetics of pancreatic cancer in the light of evolution, and we find several instances in which doing so reveals new understandings of the disease.

To set the stage for looking at pancreatic cancer in the light of evolution, we thought it would be helpful to first consider some of Darwin's own words. In the *Origins of Species By Means of Natural Selection*, Darwin wrote:

> As many more individuals of each species are born than can possibly survive; and as, consequently, there is a frequently recurring struggle for existence, it follows that any being, if it vary however slightly in any manner profitable to itself, under the complex and sometimes varying conditions of life, will have a better chance of surviving, and thus be *naturally selected*. From the strong principle of inheritance, any selected variety will tend to propagate its new and modified form [5].

This first passage succinctly encompasses the fundamental drivers through which we will examine pathology and genetics of infiltrating ductal adenocarcinoma (referred to in this review simply as "pancreatic cancer"). These evolutionary drivers include the following: (1) that more organisms are born than can survive; (2) that they compete for limited resources; (3) that the environment in which organisms live changes; and (4) that those that are best suited for their changing environment are more likely to survive. We are referring to these principles when we use the term "evolution" in this review.

These evolutionary drivers influence the development of pancreatic cancer on two levels: within the human population and within populations of the neoplastic cells themselves. Although the neoplastic cells themselves are not independent organisms, populations of cells do evolve in the face of environmental pressures, and including them in a discussion of evolution leads to new understandings of the growth and

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dissemination of pancreatic cancer. In this perspective, we start with several straightforward examples to demonstrate how the principles of evolution can be applied to human populations and to the cancers themselves, and we then end with what we hope are provocative insights generated when the pathology and genetics of pancreatic cancer are viewed "in the light of evolution." The ideas presented are intentionally simple, as our goal is to incite reflection, and for readers to apply the principles of evolution to their own work.

The second passage we include from the *Origins of Species By Means of Natural Selection* is more inspirational; one that we hope will motivate the reader to read on.

> There is grandeur in this view of life, with its several powers, having been originally breathed into a few forms or into one; and that, whilst this planet has gone cycling on according to the fixed law of gravity, from so simple a beginning endless forms most beautiful and most wonderful have been, and are being, evolved [5].

## 2 Inherited genetic variants

### 2.1 Highly deleterious germline variants *vs.* variants with small effect

The first example we will give is a very simple one, but it nicely illustrates the power of an evolutionary approach. Pancreatic cancer runs in some families, and a number of the genetic loci associated with an increased risk of pancreatic cancer have been identified [6]. Some of these loci have been discovered using candidate gene or unbiased sequencing approaches such as whole genome and whole exome sequencing, while others have been found through genome-wide association studies (GWAS) (Table 1) [6–14].

Of the established pancreatic cancer susceptibility genes, the penetrance of pancreatic cancer is highest in patients with pathogenic germline variants in *STK11*, the gene that causes the Peutz-Jeghers syndrome (Table 1) [6, 15]. The increased risk of pancreatic cancer in individuals with the Peutz-Jeghers syndrome is up to 135-fold greater than the risk of the general population [16–18]. This translates to a remarkable lifetime risk of developing pancreatic cancer of close to 60%. Fortunately, Peutz-Jeghers syndrome is extremely rare, with an incidence of between 1 in 25,000 and 1 in 300,000 births in the USA [19].

By contrast to the rare highly penetrant germline variants in the genes shown in Table 1, common variants of small effect have also been described (Fig. 1). GWAS of large numbers of patients with pancreatic cancer have uncovered a number of loci that increase the risk of pancreatic cancer, but only slightly [10, 12, 20–22]. For example, Amundadottir et al.

genotyped 558,542 single nucleotide polymorphisms (SNPs) in 1896 individuals with pancreatic cancer and 1939 controls drawn from 12 prospective cohorts and one hospital-based case-control study [8]. They found that SNP rs505922 on 9q34 was associated with pancreatic cancer (combined $P = 5.37 \times 10^{-8}$; odds ratio 1.20). This SNP maps to the first intron of the ABO blood group gene. Individuals with blood group O were found to have a lower risk of pancreatic cancer than those with groups A or B. In contrast to the rarity of the Peutz-Jeghers syndrome, 55% of the population is blood group A or B! Fortunately, the odds ratio for developing pancreatic cancer in individuals who have blood group A or B is only 1.2–1.3 [23]. As seen in Fig. 1, when the prevalence of a genetic variant is plotted against the risk it confers of developing pancreatic cancer (penetrance of the variant), a general pattern emerges, in which highly deleterious variants are significantly rarer than less deleterious variants.

Figure 1 makes perfect sense when looked at in the light of evolution. As Darwin noted, "from the strong principle of inheritance, any selected variety will tend to propagate its new and modified form [5]." The converse of this, of course, is that deleterious "varieties" will tend to be eliminated from the population. Individuals with pathogenic germline variants are less likely to survive and, as populations reach equilibrium, these variants become rare. We see this with variants in the *STK11* gene and ABO blood type. Highly deleterious germline changes, which in the case of pancreatic cancer susceptibility genes often increase risk of other lethal diseases with an early age of onset, are eliminated over time (they are rare). While "varieties" of small effect, such as those in the ABO blood group, have more limited impact on survival and are therefore eliminated more gradually (Fig. 1), one would expect that all deleterious alleles ("varieties"), unless they affect only adults long after reproduction, would eventually be eliminated over time. Some alleles that are deleterious in one way may remain in a population if they have some other, matching, benefit, such as the heterozygote advantage of sickle cell anemia in areas where malaria is endemic [24].

### 2.2 Founder effects increase risk in specific populations

We have seen that high-penetrant pathogenic germline variants are typically eliminated from the population; however, in defined populations, certain pathogenic germline variants can be frequent. For example, approximately 1% of individuals of Ashkenazi Jewish decent have a pathogenic germline *BRCA2* variant (c.6174delT) that is associated with a 10-fold increased risk of pancreatic cancer, as well as an increased risk of other cancers including cancers of the breast, ovary, and prostate [25–30]. This is in comparison to the 0.04% of the general European population that are carriers of the same variant [25–30]. Similarly, the prevalence of certain *CDKN2A*

**Table 1** Germline variants and the risk of pancreatic cancer

| Gene | % of patients with pancreatic cancer | Increased Risk | Age 50+ | Age 70 |
|---|---|---|---|---|
| SEER USA population | – | 1 | 0.05% | 0.5% |
| Hereditary non-polyposis colorectal cancer (Lynch syndrome) genes | < 1 | 7–8 | 0.4% | 4% |
| *ATM* | 1–4 | 6 | 0.3% | 3% |
| *BRCA2* | 2–7 | 2–6 | Up to 0.3% | Up to 3% |
| *BRCA1* | Up to 1 | 1–2.5 | Up to 0.15% | |
| *PALB2* | < 1 | 2.4 | 0.12% | 1.2% |
| *p16/CDKN2A* | 1–3 | 12–46 | Up to 2.3% | Up to 23% |
| *PRSS1* | < 1 | 50–60 | 3% | 30% |
| *STK11* | < 1 | 75–135 | 6.75% | Up to 67.5% |
| *TP53* | < 1 | 6–7 | 0.35% | Up to 3.5% |

+ Using the high end of the range of increased risk

variants is higher in specific populations of some countries and regions, indicating founder effects. For example, the pathogenic germline variants p.M53I, p.G101W, p.V126D, and c.225_243del are present in up to 22%, 60%, 90%, and 14% of British, Southern European, Dutch, and North American families with a pathogenic germline *CDKN2A* variant respectively [31].

Why, paradoxically, do some highly penetrant pathogenic germline variants become frequent in a population, even though they are deleterious? Again, the light of evolution provides insight into this conundrum. Consider, for instance, the *BRCA2* variant c.6174delT that is prevalent in individuals of Ashkenazi Jewish decent. Most modern-day Ashkenazi Jews are descended from as few as 350 people who left the Middle East less than 2000 years ago [32–39]. The main population expansion likely occurred after 1000 A.C.E., and this was then followed by additional population bottlenecks in the Middle Ages [32–36, 39]. Ashkenazi Jews who survived these bottlenecks contributed a large percentage of the gene pool present in present-day Ashkenazi Jews. The *BRCA2* c.6174delT germline variant likely arose in an Ashkenazi Jew 29 generations (~ 750 years) ago [37–39]. It is likely that this initially rare germline genetic variant passed through one of the bottlenecks and, in so doing, remained in a significant percentage of the Ashkenazi Jewish population (Fig. 2) [32–36].

## 3 Somatic mutations in primary cancers

Our cells accumulate large numbers of mutations every day. There are ~ 37.2 trillion human cells in the human body, and most of these cells divide on a regular basis [40–44]. For example, each human produces around $10^{11}$ (100,000,000,000) new blood cells and billions of other types



**Fig. 1** Graphical representation of variants associated with risk of pancreatic cancer. Graph shows pancreatic cancer risk and prevalence of germline variant in patients with pancreatic cancer. Not all variants associated with risk of pancreatic cancer are shown. Size of each circle represents the prevalence of variant in general population. Rare high-risk variants in red. Common low-risk variants in green
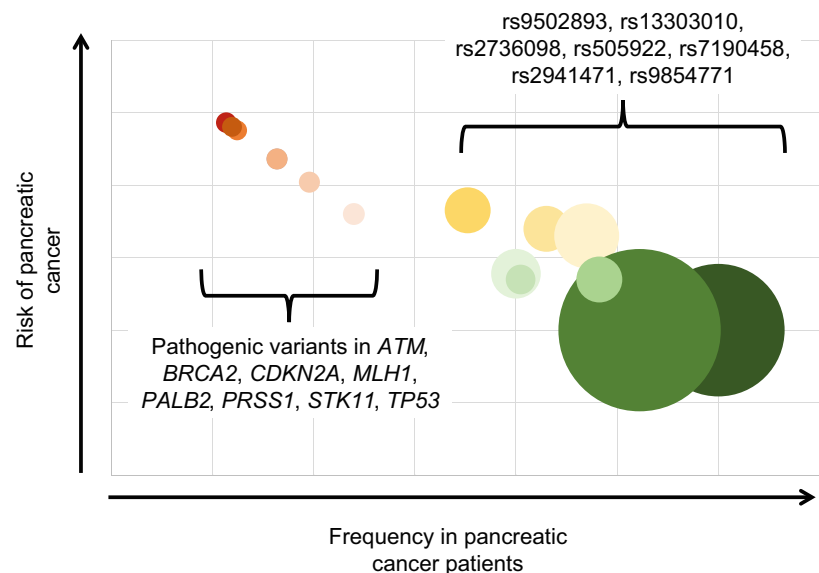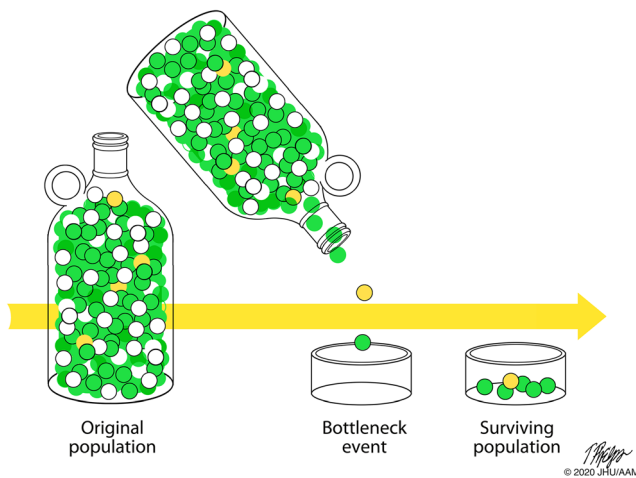
**Fig. 2** The prevalence of a rare genetic variant (yellow balls) will increase significantly if it happens to pass through a population bottleneck

of cells each day [45]. As cells divide, they need to copy their DNA, and when they do, two to ten mutations are estimated to occur per diploid genome per cell division [46–48]. Multiply this by the billions of cells undergoing division in our bodies each day, and the result is the accumulation of billions of somatic mutations each day!

It should therefore not be surprising that cancers harbor large numbers of somatic mutations [49–51]. Recent whole genome sequencing of large series of pancreatic cancers identified an average mutational burden of one somatic mutation per 2.64 Mb (range 0.65–28.2 per Mb), where the vast majority of the mutations are passenger mutations [52]. This raises several thought-provoking questions that, again, are best answered in the light of evolution.

### 3.1 Why do our cells accumulate these somatic mutations?

Why, with billions of years of evolution to perfect DNA replication, do our cells still make so many errors? Why don't cells correct somatic mutations as they occur? The answer is simple when viewed in the light of evolution. Imperfect DNA replication allows for evolution to occur. If we copied our germline DNA perfectly, we would never be able to evolve; we would still be slime on a primordial pond! In addition, proof-reading DNA replication is costly to cells in terms of energy and time (Fig. 3) [53, 54]. Gradual improvement in the fidelity of polymerases would also work against the goal of evolving a perfect polymerase: selecting for higher fidelity polymerases decreases the mutation rate, thereby preventing new mutations that would be required in order to increase the fidelity of the polymerases even further [55]. Simply put, mutation rates reflect an evolutionary balance between the costs and benefits of allowing mutations to accumulate [53].



**Fig. 3** Proof-reading DNA replication is costly to cells in terms of energy and time

### 3.2 Why doesn't our immune system eliminate all neoplasms?

Our immune system can be effective in eliminating early neoplasms, so why doesn't it eliminate all neoplasms [56]? The answer is, in part, because our immune system is also a product of evolution. As our immune system has evolved, it has faced the evolutionary balance between immune surveillance and autoimmunity [57–59]. Our immune system has evolved to recognize certain antigens and not others. Diversity of antibodies and T cell receptors has evolved to neutralize an ever-changing variety of pathogens, and negative selection has evolved to prevent the recognition of self-antigens. The recognition of too many epitopes can lead to autoimmunity, and failure to recognize antigens can lead to infections and to the emergence of a cancer [60]. Individuals who are born with a stronger immune system will be better able to fight infections (and cancer), while those who are born with a weaker immune system will be less likely to develop autoimmune diseases. Those individuals with an immune system, as Darwin wrote, "in any manner profitable to itself," will have a better chance of surviving. When viewed in the light of evolution, the immune surveillance of cancer is therefore imperfect, because natural selection balances the benefits of immune surveillance with the costs of autoimmunity [57, 61]. Conversely, as cancers develop, the neoplastic cells that successfully evade the immune system will be selected

for and we would predict that advanced cancers would be relatively resistant to immunotherapies [56].

## 4 The emergence of resistant clones after targeted therapy

The emergence of resistance has been recognized as a major clinical problem in the treatment of infectious diseases since antibiotics were first developed. The treatment of tuberculosis in the 1950s and of human immunodeficiency virus (HIV) in the 1990s are great examples [62]. The same holds true for the treatment of cancer [3, 63–66]. Resistance often emerges quickly under the selective pressures of targeted therapies, as cells with genetic variants that provide resistance against the therapy will have an increased fitness and will be selected for (Fig. 4). For example, some melanomas are driven by somatic BRAF gene mutations, and the introduction of effective BRAF inhibitors offered great hope for the treatment of melanoma. Unfortunately, although great initial responses were seen in human trials, melanomas treated with only a targeted BRAF inhibitor almost always recurred [67]. Remarkably, in some patients with multiple metastases, essentially, every single one of the many metastatic nodules recurred [67].

We can anticipate the same problem with targeted therapies for pancreatic cancer. Some pancreatic cancers with biallelic inactivation of the BRCA2 gene respond dramatically to poly (ADP-ribose) polymerase (PARP) inhibitors [68–70]. But experience has shown that when cancers with biallelic inactivation of BRCA2 are treated with an agent that exploits this genetic vulnerability (such as a PARP inhibitor), clones will emerge that harbor additional intragenic BRCA2 mutations that restore the reading frame and in so doing restore BRCA2 function [69, 71]. These cells with secondary mutations in BRCA2 will be resistant to therapy and they will grow, leading to the emergence of clinical resistance to that targeted therapy.
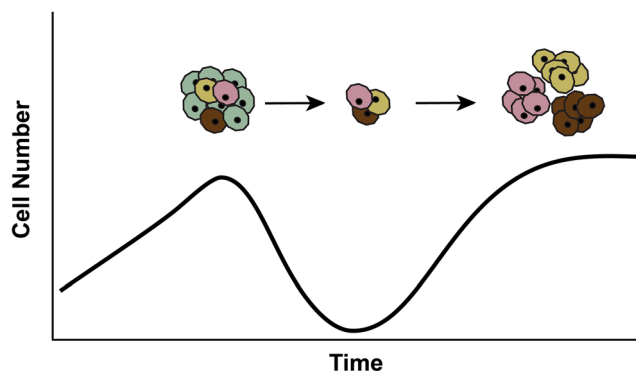


**Fig. 4** Although therapies may successfully kill most of the neoplastic cells, small populations of pre-existing neoplastic cells with genetic alterations that allow them to survive the selective pressure of the therapy will emerge to form drug-resistant clones

The mutations that arise in patients with recurrent and metastatic PDAC after other therapies are only beginning to be characterized [72]. Some of these mutations arise in genes rarely if ever mutated in primary untreated pancreatic cancers. Not surprisingly, these mutations are typically were present in pre-existing clones and provide additional oncogenic advantage or help to overcome environmental pressures such as targeted therapies. Examples of such mutated genes include genes coding for members of the MEK-ERK pathway and for the PI3K-MTOR pathway [72]. Finally, heterogeneity of mutated driver genes can exist within different metastatic clones, indicating that different tumor microenvironments can drive the selection of distinct subclones which may result in different adaptations to targeted therapies in different metastatic sites [72].

This emergence of resistance can be understood when viewed with the light of evolution. Advanced cancers are the products of hundreds to thousands of cell generations and contain a billion to a trillion ($10^{12}$) cells. By chance, one of these billions of cells is likely to acquire a somatic genetic alteration that makes that cell and its descendants resistant to a targeted therapy [73]. These resistant cells will remain a small subpopulation in the cancer until the patient is treated with the targeted therapy (Fig. 4). Targeted therapies effectively kill vulnerable cells, creating powerful pressures that select for clones that have acquired resistance to the therapy. Again, quoting Darwin, "it is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adapted to its present environment [5]." Targeted cancer therapy provides a powerful selective environment for cancer cells which happen to have a mutation that confers resistance to the therapy.

The lesson that evolution teaches us here is the same taught when single agents were first used to treat tuberculosis or HIV [62]. Single agents for these diseases will not succeed, as only a single mutation can quickly lead to the emergence of resistant clones. Single-agent targeted therapies to treat pancreatic cancer will similarly fail. Combination therapies that incorporate agents that target distinct pathways are more likely to succeed as it is unlikely that pre-existing clones exist in a cancer that have mutations that simultaneously confer resistance to multiple different therapies. Taking it one step further, Walther and colleagues have suggested that lessons from the extinction of species can be used to guide novel approaches to drive tumors "to extinction [74]."

## 5 Provocative thoughts

In addition to the more obvious examples given above, the light of evolution can provide provocative insights into the biology of pancreatic cancer.

## 5.1 Traits should not be considered in isolation

Darwin emphasized that a trait that provides a selective advantage in one environment may not provide a selective advantage in another (Fig. 5):

> …when a plant or animal is placed in a new country among new competitors…the conditions of its life will greatly be changed in an essential manner. If we wished to increase its average numbers in its new home, we shall have to modify it in a different way to what we should have had to do in its native country [5].

If we apply this reasoning to the progression of pancreatic neoplasia, we can see that genetic alterations that are important in the development of precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN) lesions and intraductal papillary mucinous neoplasms (IPMNs), may no longer be important when that same cell, or its descendants, have metastasized and are present in a completely different environment, such as in the liver [3, 65, 75]. Traits that give a cell a survival advantage in the confines of a duct in the pancreas are unlikely to provide the same survival advantage in the dramatically different environment of the liver. For example, an activating point mutation in KRAS may provide a survival advantage to a cell in the pancreatic duct [76–80]. This cell may then grow into a PanIN lesion and subsequently into an invasive carcinoma which then metastasizes to other organs [81]. All of the cells in the metastases will harbor an identical KRAS mutation, but, as observed in experimental models, this doesn't mean that the neoplastic cells in their new environments are still necessarily dependent on mutant KRAS for their

growth advantage [82, 83]. This possibility has significant implications for targeted therapy, as, for example, the impact of targeting KRAS in distant organs may be very different from that of targeting KRAS in PanIN lesions [84, 85].

Another striking example of this phenomenon is the distinct prevalence of mutations in specific driver genes at different stages of tumorigenesis. Some driver genes, such as TP53 and SMAD4, are mutated at much higher prevalence in advanced precursor lesions and invasive carcinomas, suggesting that selection for these mutations is limited to late in pancreatic tumorigenesis [86]. In contrast, recent studies have demonstrated mutations in other driver genes at a higher prevalence in early neoplasia. For example, mutations in RNF43 occur at higher prevalence in noninvasive IPMNs than in invasive carcinomas associated with an IPMN, suggesting that the mutations are selected during precancerous neoplasia but selected against in the subclone that eventually invades [87]. Similarly, hotspot mutations in KLF4 occur at higher prevalence in low-grade IPMNs than in high-grade IPMNs and are frequently limited to low-grade regions in IPMNs with both grades [88]. These observations suggest that KLF4 mutations are selected for in low-grade IPMNs but selected against during progression to high-grade dysplasia. However, the mechanisms and evolutionary drivers underpinning this differential selection have yet to be identified.

## 5.2 Phenotypic and genetic drift can be confused for growth advantage

Not all of the phenotypes and genotypes observed in a population provide a selective advantage [89–92]. Genetic drift describes the random fluctuations in gene variants in a population, due to the random sampling when a variant is passed on



**Fig. 5** A trait that provides a selective advantage in one environment (white fur in the snow) may not provide a selective advantage in another (white fur on green grass)
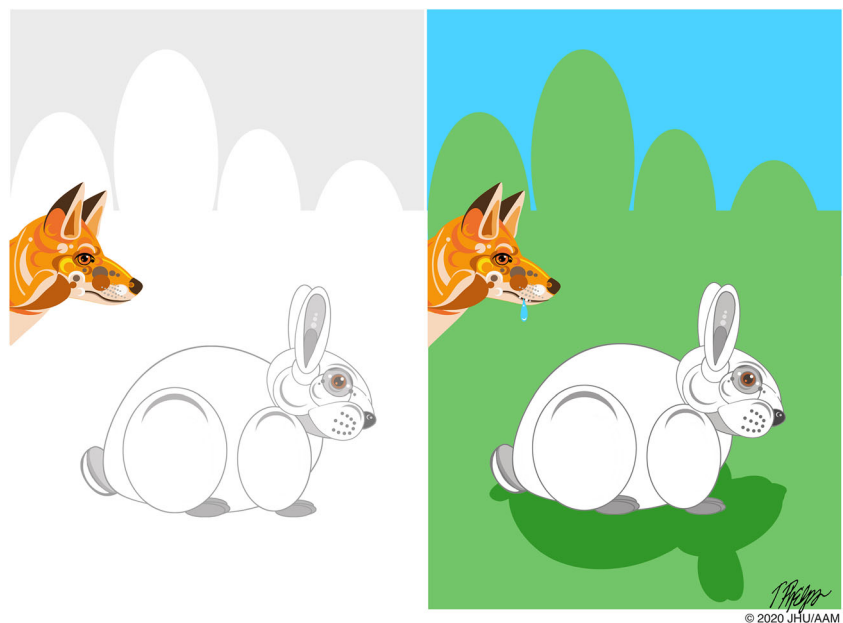
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from one generation to the next. As shown in Fig. 6, genetic drift is most easily detected when individuals are isolated from the main group.

Extending this to pancreatic neoplasia, we can surmise that not all of the genotypes and phenotypes we observe in a tumor have clinical or biological significance [90]. For example, if we are therapeutically targeting a genetic change that is present in one area of a cancer, we need to realize that this genetic change may well be a passenger mutation that occurred late in the development of the invasive cancer [48, 90, 93, 94].

This problem is illustrated in the hunt for genetic alterations that "drive" metastases. A number of investigators have looked for drivers of metastases by comparing the genetic changes in metastases to paired primary lesions from the same patients [95]. This approach assumes that any genetic changes in the metastases and not in the primary lesion must be promoting the metastases. While it is human nature to assume that any differences are causal, Darwinian principles tell us that we must also consider chance spread with genetic drift (Fig. 6). Indeed, although there are differences between metastases and primary lesions, no "metastasis gene" has yet been discovered [80, 95]. This perhaps should not be surprising as D. Shibata and colleagues have shown, using multiregional sequencing of invasive colon cancer, that barriers to invasion are minimal, suggesting that there aren't "late bottlenecks" in cancer evolution [96].

The same is also true for phenotypes. When pathologists look at histologic sections, many of the morphologic changes observed will not have biological or clinical significance. For example, some pancreatic cancers have a "clear cell" and others a "foamy gland" appearance [97, 98]. While these distinctive appearing cancer types have caught the eye of pathologists, they have no known biological or clinical importance.

Even though many features do not have an adaptive advantage, it is human nature to ascribe significance to each feature we observe.

## 5.3 We do not completely understand gene-environment interactions

The selective pressures placed on a species by its changing environment are difficult to comprehend fully [99]. As Darwin wrote, "we are much too ignorant in regard to the whole economy of any one organic being, to say what slight modifications would be of importance or not… we may sometimes attribute importance to characters which are really of very little importance, and which have originated from quite secondary causes, independently of natural selection [5]."

The complexity of interactions with the environment are highlighted in pancreatic cancer. It was assumed for years that the intense desmoplastic stroma elicited by invasive pancreatic cancers is bad for the patient, that it prevents therapies from reaching the cancer cells, and that if we could only eliminate the stromal environment, we would be able to cure the cancers [100]. Unfortunately, the role of the stroma, the "environment" of pancreatic cancer, has proven enormously complex in pancreatic cancer [100, 101]. Some attempts to reduce the stroma have actually promoted tumor growth and metastases [102]. Moreover, recent work suggests that pancreatic cancer cells that have invaded back into the ductal system are less responsive to chemotherapy than cancer cells in the stroma [103]. We clearly do not fully understand the gene-environment interactions that drive pancreatic cancer.

## 5.4 Most "varieties" never emerge through all of the bottlenecks

We can learn from evolution that many new variants are initiated but the promotion of a variant to a separate species is rare (Fig. 7). By analogy, humans develop a large number of precancerous neoplasms, and yet most of these neoplasms never progress through all the bottlenecks to invasive carcinoma. Simply put, as we age, neoplasms are commonly or even ubiquitously initiated but promotion to full malignancy is rare [104–106].

**Fig. 6** The chance survival of one member of a population can lead to genetic drift. Sampling that population at a later date may give the erroneous impression that the population was selected for because it had a survival advantage

**Fig. 7** Most "varieties" never emerge through all of the bottlenecks. Pictured are *Titanis* known as the "terror" bird, a shoebill stork, and the dodo. All are extinct except for the shoebill

This has profound implications for the early detection of early pancreatic neoplasia as most of the precancers detected will never progress to invasive cancer, and we face a real risk of over treating these clinically harmless precursor lesions [107]. For example, 54% of "normal" adult pancreata have at least one PanIN lesion [108], and 2.6% of patients without pancreatic symptoms have a pancreatic IPMN detectable on computerized tomography scanning [109]. Clearly, the vast majority of individuals with one of these precancerous lesions will never develop invasive pancreatic cancer [110]. Yet, when we detect these lesions, there is a natural desire to remove them, and, as a result, some patients are over treated [111–113].

This variation in the behavior of precancerous lesions is reflected in the significant genetic heterogeneity within and among precursor lesions. Wood and colleagues carefully microdissected invasive cancers that arose in pancreata with a well-defined intraductal papillary mucinous neoplasm (IPMN) and found that IPMNs are genetically heterogeneous and that the invasive cancers sometimes were genetically unrelated to the IPMNs [76, 87, 114, 115]. Thus, it is clear that some pancreata harbor many heterogeneous noninvasive neoplastic clones and that only a small fraction of these clones progress to invasion [116–118]. Within these precancerous neoplasms, some patterns in the genetic heterogeneity can be discerned. For example, heterogeneity with respect to mutations in the initiating driver gene *KRAS* and *GNAS* occurs in IPMNs with low-grade dysplasia, indicating polyclonal origin [114]. In contrast, high-grade IPMNs often contain monoclonal populations of neoplastic cells, but subclones within these populations contain different mutations in the same tumor suppressor gene. In particular, this pattern has been described in mutations in the tumor suppressor gene *RNF43*. A single IPMN can acquire multiple *RNF43* mutations, each limited to a distinct subclone. This pattern suggests parallel evolution with respect to these mutations, i.e., the independent evolution

of similar features due to common function, in this case in distinct neoplastic subclones [87, 114, 119]. Taken together, these findings suggest complex selective pressures that vary throughout the different stages of preinvasive pancreatic neoplasia. This genetic heterogeneity is counterintuitive to a simpler model of a series of sequential mutations in oncogenes and tumor suppressor genes that invariably progresses to an invasive cancer. Still, emerging data suggest that premalignant tumorigenesis occurs *via* waves of clonal diversity, followed by bottlenecking, as strongly selected driver mutations arise during the carcinogenic process [87, 114, 119]. Finally, invasion can also be considered as a founder effect: a cell escapes the highly competitive and heterogeneous environment of the precursor lesion, to find new resources and space to grow. The lack of clonal heterogeneity in invasive cancer and metastases might indicate that this is the last bottleneck.

Although most invasive pancreatic cancers are extremely aggressive, we also cannot completely rule out the unlikely possibility that some minimally invasive pancreatic cancers will not metastasize during the life of the patient. This is nicely illustrated with thyroid cancer, where increased screening has led to the detection and removal of many invasive cancers, but has not reduced the mortality from the disease [120, 121]. It appears that many of the thyroid cancers detected on screening would never have harmed the patient. In the case of the pancreas, the jury is still out as to whether the detection of early, stage I, cancers arising in association with an IPMN saves lives [122].

## 6 Conclusions

It has been more than 185 years since Charles Darwin first set sail on the Beagle, and over 160 years since his masterpiece the *Origins of Species By Means of Natural Selection* was first published in 1859. Darwin's theory of evolution by means of natural selection is arguably one of the most important ideas ever put forth in the life sciences. The principles laid out by Darwin continue to provide insight into all aspects of biology. Here, in some small way, we hope we have convinced you that "thinking evolutionarily" can provide insight into modern pancreatic genetics and pancreatic pathology.

Since we began with passages from Darwin, we thought we should end with Darwin's words.

"The distribution of tenants of this archipelago would not be nearly so wonderful, if for instance, one island has a mocking-thrush and a second island some other quite distinct species... But it is the circumstance that several of the islands possess their own species of tortoise, mocking-thrush, finches, and numerous plants, these species having the same general habits, occupying

analogous situations, and obviously filling the same place in the natural economy of this archipelago, that strikes me with wonder" (journal written on the Beagle 1831-1835 [5]).

These words prompt us, as pathologists and pancreatic cancer researchers, to more carefully study the complex varieties of pancreatic neoplasms. It is in doing so that we may gain unique insight into this terrible disease.

## Declarations

**Conflict of interest**   Ralph Hruban has the potential to receive royalty payments from Thrive Earlier Diagnosis for the GNAS invention. The other authors declare that they have no competing interests.

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