Commentary
DOI 10.1007/s12038-012-9199-1

From aneuploidy to cancer: The evolution of a new species?

1. Introduction

In his book *Die mikroskopische Diagnose bösartiger Geschwülste,* David Hansemann proposed in 1897 that during the transformation of a normal cell to a cancer cell, 'the cell change[s] [its] character in every regard morphologically and physiologically to a new species'. For more than a century now this idea has not received much attention, although increasingly striking parallels between evolutionary processes and cancer development have been acknowledged. This commentary aims to take a closer look at the 'cancer as a species' theory, with regards to another long abandoned but closely related thesis about cancerogenesis by Theodor Boveri. In this theory, he described an asymmetrical distribution of chromosomes during mitosis resulting in aneuploidy as the starting point for tumorigenesis.

Based on the Hansemann–Boveri hypothesis and its implications for the perception of cancer as an own species as well as the modern concepts of species and the current views on asexual speciation, we hypothesize that cancer cells are not a new species; however, each cancer cell has started to undergo a process of speciation. This hypothesis is made under the assumption that successful evolution of species is defined by bacteria or *Saccharomyces cerevisiae*, which show strong parallels to the development of infectious cancers.

In 2008 alone, an approximate number of 12.7 million cancer cases and 7.6 million cancer deaths have been reported worldwide (Jemal *et al.* 2011), making cancer the leading cause of death in developed countries and the second leading cause of death in developing countries (The World Health Organization 2008). Even after more than 100 years of cancer research and despite enormous efforts, the cause of cancer remains unclear (Li *et al.* 2000; Pihan and Doxsey 2003; Steinberg 2004; Storchova and Pellman 2004; Duesberg *et al.* 2006; Pathak and Multani 2006; Bannon and Mc Gee 2009; Bozic *et al.* 2010). One of the first theories regarding the origin and nature of cancer was developed by Hansemann in 1897 and taken up by Boveri in 1914. Both believed that the starting point of malignant transformation was found in major genetic alterations, also referred to as aneuploidy. Aneuploidy is defined as 'the chromosomal constitution of cells which deviate from the normal by the addition or subtraction of chromosomes, chromosome pairs, or chromosome fragments' in the National Library of Medicine (NLM)-controlled vocabulary database (Mesh). Aneuploidy changes the character of a cell in a way that crosses species borders and thus makes cancer a species of its own (Hansemann 1897; Boveri 1914).

In an aneuploid cell, for instance, in a tumor cell, thousands of genes (Klein *et al.* 2007) and the expression of the proteins they are coding for are altered, resulting in an entirely new phenotype. This change in gene expression also disturbs the delicate process of segregation, synthesis and repair of chromosomes. A genomic instability is introduced, which gives birth to daughter cells with an ever-changing karyotype, thus making cancer development an evolutionary process. By assuming aneuploidy as the cause of cancer progression, the hallmarks of cancer (Hanahan and Weinberg 2000) and other intrinsic properties of cancer, such as the long 'neoplastic-latencies', can be explained (Li *et al.* 1997; Duesberg and Rasnick 2000;Li *et al.* 2000; Duesberg *et al.* 2004; Kops *et al.* 2005; Duesberg *et al.* 2006; Pathak and Multani 2006; Chi and Jeang 2007). In a very recent publication, aneuploidy is proposed to be the explanation for the main characteristics of cancer cells: autonomy, karyotypic individuality and flexibility, as well as immortality. The authors also pointed out the similarity between the role of aneuploidy in tumorigenesis and speciation, defining cancer as an own species (Duesberg *et al.* 2011).

Keywords. Aneuploidy; genetic speciation; infectious cancer; karyotype; tumorigenesis

Published online: 19 April 2012

Despite the 'cancer as an own species' idea being proposed a century ago, it is very seldom addressed in recent literature (Duesberg and Rasnick 2000; Li *et al.* 2000; Duesberg *et al.* 2011). Only rarely have attempts been made to systematically analyse this hypothesis in the light of modern species theories (Vincent 2010). One of the challenges of trying to find an answer to whether cancer qualifies as a new species is the heterogeneity found within different species definitions.

In this commentary we aim to re-examine the recent species definitions and apply these to the case of cancer to decide whether cancer can be seen as a new species. The difficulties of merging the common characteristics of cancer cells such as clonal heterogeneity and genetic instability with the concept of species and speciation will then be discussed. In this context, we will then proceed to clarify the role of aneuploidy of cancer cells. However, testing the cancer as a species theory with current species definition shows many parallels and inconsistencies as well. These inconsistencies can be resolved if we presume that cancers or cancer cells are not a species of their own but rather show the characteristics of a developing species.

2. Species definition

When trying to determine what separates one species from another, it very quickly becomes clear that there is hardly a concept in modern biology as controversial as the concept of species. Although the Linnaean concept of species as one of the fundamental units of comparison (Linnaeus 1767) is widely accepted, the question of which characteristics are sufficient to differentiate between species is still a major topic of discussion (Templeton 1989). Having many alternative, often incompatible, definitions of species leads to different species taxa depending on which concept is chosen and which characteristic is thought to be the determining factor in differentiating between species. A common definition of species as 'a group of living organisms consisting of similar individuals capable of exchanging genes or interbreeding' (*Oxford American dictionary*) is based on the species definition by Ernst Mayr. Mayr was one of the first and still most influential advocates for a modern concept of species. In his biological species concept (BSC), he claimed that 'species are groups of actual or potentially interbreeding natural populations, which are reproductively isolated from other such groups' (Mayr 1942). The often-addressed disadvantage of this definition is its inapplicability to asexually reproducing life forms.

A broader species definition by de Queiroz takes the 'existence as a separately evolving metapopulation lineage as the only necessary property of species'. 'Metapopulation lineage' is defined as a group of connected subpopulation sharing an ancestral-descendent succession. A species being phonetically distinguishable, monophyletic, reproductively isolated or dependent on different ecological niches and all the other defining needs of the former concepts are therefore properties that species may or may not acquire. Also, these properties may or may not be defining for an own species, depending on whether the result is a lineage 'evolving separately from other such lineages' (de Queiroz 2005). However, to ensure the separate evolution of a meta-population lineage without diverging into different meta-population lineages with different and separate evolutionary fates, there must be a mechanism of cohesion. In Mayr's BSC this mechanism of cohesion is the constant gene exchange due to interbreeding. Since this concept cannot be adapted to non-sexually reproducing organisms, a more general mechanism is needed. In his cohesion species concept (CSC),[1] Templeton advocates different forces of cohesion (genetic drift with natural selection and gene flow) to ensure genetic similarity and thereby a common evolutionary fate (Templeton 1989).

However, the above-mentioned species definitions have limitations in defining asexually reproducing species. In order to test the 'cancer as a species' hypothesis, one has to rely on a concept of species that can also be applied to asexually reproducing species, such as bacteria and possibly cancer cells.

There has been a great debate on how to classify bacterial species (Goodfellow *et al.* 1997). It is well accepted that bacteria can be organized in some sort of phenotypic or genetic clusters (Cohan 2002). However, the differentiation between bacterial species is not distinctly defined (Doolittle and Papke 2006):

[1] Note that CSC is a subtype of the evolutionary species concept (ESC) which states species as *'an entity composed of organisms which maintains its identity from other such entities through time and over space, and which has its own independent evolutionary fate and historical tendencies'* (Mayden 1997).

gene exchange is promiscuous between different species (Cohan 2002), bacterial species contain different ecotypes (Cohan 2001) each with properties of a species, and there is no agreement over which properties a 'genetic cluster' should have in order to be called a species. To answer the question what bacterial species are, Frederick Cohan based his work on Templeton's CSC and argued that '(a) species is a group of organisms whose divergence is capped by a force of cohesion; divergence between different species is irreversible and different species are ecologically distinct' (Cohan 2002). This definition gives a better answer to the question if two 'clusters' with a common ancestry, as is the case with cancer, can be seen as distinct species, then the >70% average nucleotide identity (ANI) cutoff line proposed by Wayne *et al.* in 1987 (Wayne *et al.* 1987) or the 3% divergence cutoff in 16S rRNA found by Stackebrandt and Goebel (1994). The difficulty with the latter is that '…justifiable species may be found, even among strains that show higher than 98–99% ANI, when severe ecological constraints, which dramatically affect the phenotypic and ecological potential of the organism, have occurred' (Konstantinidis *et al.* 2006). In the case of asexually reproducing species, the mechanism of cohesion would consist of 'intermittent bouts of natural selection' following mutation, recurrently resetting the genetic divergence within the population to zero (Cohan 2002). A mutant in the population would either be successful, driving all other organisms of the same species to extinction, or vanish due to unfitness. In both cases, no new species evolves and the genetic coherence within the population of a species is ensured [as shown by Ferea *et al.* (1999) in asexual experimental populations of *Saccharomyces cerevisidae*]. These recurrent events restraining the genetic variation, also seen in cancer cell populations (Merlo *et al.* 2006), are called 'periodic selection' (Atwood *et al.* 1951).

However, if the mutant coexists with its predecessors, e.g. occupies a new niche due to micro-environmental changes, and the new population formed by this mutant 'cannot be extinguished by (other) adaptive mutants from its former population', a new species has evolved. In this case, no force of cohesion caps the genetic divergence between these populations (Cohan 2002).

The question that follows this conclusion is how, if at all, can a new species evolve through minor genomic changes? The answer for highly sexual eukaryotes surely is allopatry (i.e. that the new species and its former population inhabit different geographical regions) (Mayr 1963; White 1978), whereas for bacteria genetic recombination between different species or ecotypes could be the answer (Cohan 2002). For asexual eukaryotic cells this mechanism of speciation could lie in the introduction of aneuploidy (King 1987; Dunham *et al.* 2002; Duesberg and Rasnick 2000) and or in changes of the micro-environment. Supporting this theory is the fact that it is well demonstrated that the evolution of a new species is based on karyotype differentiation (Yosida 1983; 1973; White 1978; Matthey 1973) and the definition of a species lies in its specific karyotype (O'Brien *et al.* 1999).

Despite of numerous differences between eukaryotic and prokaryotic cells, there are many characteristic similarities between cancer cells and bacteria, making bacterial species definitions more applicable to cancer cells than species definition for eukaryotic sexually reproducing species. Firstly, both cell types are characterized by a mainly asexual reproduction mechanism, with low, in most cases, almost inconsiderable rates of recombination between different cells (Cohan 2002). Secondly, they both lack a convenient supracellular organization (Huxley 1956; Duesberg and Rasnick 2000; Stemmler 2008), making them both fit within a species definition with a broader, population-based point of view than, for instance, the BSC would have. By applying a bacterial species concept to cancer, a change in the perspective on the human body, and the cancer within, has occurred. Instead of seeing the whole human body as a metazoan belonging to a particular species, the focus is shifted to a cellular level where the decision, whether something is a new species or not, has to be made from cell to cell. Although this is a dramatic step, we think it is reasonable, since one of the main characteristics of cancer cells is that they do not act as part of a multicellular compound anymore. It is surely not accidental that an attribute unifying most cancer types is a dramatic change in cell adhesion and communication. Accepting cancer as a cellular disease, as proposed by Virchow (1859), and applying a bacterial species concept, the views on 'normal' cells have to change as well. There is no sense in comparing a sexually reproducing multicellular organism, like the human when looked at as a whole organism, with an asexually reproducing unicellular organism, like cancer might be (Huxley 1956; Pathak and Multani 2006; Merlo *et al.* 2006; Vincent 2010). If we apply the CSC to test the 'cancer as a species' hypothesis to evaluate if cancer is a justifiable own species, the cancer cell is not compared to the human as a whole but to every single human cell. The human cell is regarded as an

independent organism living in a compound cooperating with others, as already described by Virchow (1859). Seeing the human organism as a group of cooperating entities, the problem that arises is that these entities each are competitors of the cancer cell, but as a whole they form the environment in which the cancer cell is developing. This dualism drives most cancer species finally to extinction – by 'winning' the evolutionary battle and out-competing the 'normal' cells; however, cancer does also destroy its own environment. Still, this is no hindrance to the 'cancer as species' thesis – the human species is constantly destroying the only environment they can live in – but shall be the starting point of an argumentation in favour of a description of cancer as a process of speciation.

Assuming that cancer development is an evolutionary process (Gartler 1968; Heneen 1976; Nelson-Rees *et al.* 1980), it should be possible to apply the same criteria used to determine whether a newly evolving bacterial clone in a population is a species of its own to a population of eukaryotic cells, such as the human body and the newly evolving cancer cell within. Applying Cohan's bacterial species definition in a cell population two separate species exist if the genetic divergence of the subpopulations is not hindered by a 'periodic selection event' in one of the two subpopulations, driving the less adapted clonal population to extinction and thus resetting the genetic variation between the subpopulations to zero.

When evaluating cancer development with this set of rules, it becomes clear that cancer cannot be regarded as an own species. In the population of eukaryotic asexually reproducing single cellular organisms, the evolving genetically differing clone forming a cancer is still competing with its ancestors within the human body, finally driving them to extinction. If this were not the case, cancer would not be a lethal disease.

What if we put aside the fatal fact that by competing with its ancestors the cancer cell does also destroy its environment, and replace the 'animal environment' by an artificial one, making the setting even more similar to a bacterial population in culture described by Cohan? This has been done with the HeLa cells. As described by Cohan, the HeLa cells proved to be very successful for an adaptive bacterial clone in driving other human cell lines to extinction (Gartler 1968; Heneen 1976; Nelson-Rees *et al.* 1980) and thus resetting the genetic divergence within the population to zero, not taking into account the genomic instability brought by the aneuploidy of HeLa cells. These findings suggest that HeLa cells, as well as other cancer cells, cannot be defined as a new species using the bacterial species concept by Cohan.

However, the aneuploidy, also seen in HeLa cells, remains the main obstacle to the 'cancer as a species' thesis, no matter which concept is applied. It makes no sense to discuss the different characteristics to distinguish between two 'separately evolving meta-population lineages' if there is not an established lineage, i.e. a strict 'ancestral-descendant sequence', due to the 'notorious instability' of cancer cell karyotype. It seems obvious that the first requirement for a new species, i.e. 'a group of organisms whose divergence is capped by a force of cohesion' (Cohan 2002), is a more or less stable karyotype. In the case of cancer this force of cohesion, on the one hand, binds the tumour to the 'normal' human cell, in most cases finally leading to its own extinction, but on the other hand, cannot prevent the increase of total diversity in the neoplastic population (Merlo *et al.* 2006). This seems contradictory; however, it is only logical if cancer and cancer development is not seen as a new species but as a speciation event of a unicellular organism.

In a more recent work, Mark Vincent also based his theory of cancer as a new species on the current concepts of bacterial species, seeing similarities between tumour development and bacterial populations. Vincent argues that 'the tumor genome may be swept clean and homogeneity reestablished by a form of genetic cohesion, as with bacteria' and cancer would thus fulfill the CSC criteria for a new species. He claims that the justification for bacterial species can also be adapted to cancer, so that cancer cells can be considered a new species, or in his eyes, 'not just a single species different from its host, but a whole series of species different not only from its host but also from each other'. By defining cancer cell populations not as a single species but a whole 'collection of unicellular eukaryotic organisms that are fully capable of existence independent of each other' (Vincent 2010) and not even belonging to the same species, he solves the hurdle of tumour cell heterogeneity to the species concept. In his article Vincent also addresses the very interesting resemblances of structures and pathways essential for the maintenance of a multicellular animal and those involved, or rather de-regulated, during tumorigenesis, such as Hedgehog, Wnt, Notch and BMP or Cadherins (Rubin and de Sauvage 2006; Rokas 2008; Stemmler 2008). Therefore, 'it is probable that the nature of cancer is to be found in the derangements of those acquired aspects of the eukaryotic cell that enable multicellular life' (Vincent 2010). Vincent then concludes that cancer development could be a

'phenomena […] [that] might have become activated not as an 'accident', but as an entrenched survival mechanism in response to existential genotoxic environmental stress'.

If we would accept cancer as a unicellular eukaryotic species 'use[ing] only a minute fraction of the information of their normal predecessors to establish a primitive form of autonomy similar to that of microbes' (Duesberg *et al.* 2011), it follows that every cell has the potential to be the starting point of the evolution of a new unicellular species in order to adapt to existential genotoxic environmental stress.

For all that, even if cancer is not seen as a single species but a whole bunch of different (unicellular) species, like Vincent proposes, there are hardly two cancer cells with exactly the same genome, although it has recently been shown that there are quasiclonal carcinomas in mice with 'total chromosome numbers oscillat[ing] 5-20% around clonal averages' (Klein *et al.* 2010). These effects are even seen in cells grown in culture for some time. The 'notorious instability' of the cancer cell genome (Nowell 1976; Duesberg and Rasnick 2000) still remains the main obstacle to the 'cancer as species' theory, if cancer is described as an own species. This is no obstacle if tumorigenesis and cancer development is seen as a process of speciation. We therefore hypothesize that tumorigenesis is an ongoing speciation event of a unicellular eukaryotic species that begins as a result of environmental stress. The importance of aneuploidy in this process as the motor of speciation has been mentioned above but shall now be further discussed.

3. Aneuploidy and cancer

It is this striking parallelism between the mechanism of speciation and one of the main characteristics seen in the vast majority of solid tumour, i.e. aneuploidy (Li *et al.* 1997, 2000; Duesberg and Rasnick 2000; Duesberg *et al.* 2000, 2004, 2006; Storchova and Pellman 2004; Pathak and Multani 2006; Chi and Jeang 2007), that led to the idea of cancer as a new species (Duesberg and Rasnick 2000; Pathak 1990). There is a heated debate ongoing about the question whether aneuploidy is the primary cause of cancer development or only a secondary side effect of a process started and upheld by somatic mutation. Even if it is assumed that aneuploidy, which has the strongest correlation to malignant tumorigenesis (Duesberg *et al.* 2006), is the necessary condition for cancer development, there still is no consensus over how the process of progressing aneuploidy is started. One idea is that an unspecific aneuploidy is introduced 'either by carcinogens or spontaneously' (Duesberg and Rasnick 2000; Duesberg *et al.* 2006), whereas there are others suggesting that somatic mutation (Pihan and Doxsey 2003; Schneider and Kulesz-Martin 2004; Michor *et al.* 2005; Li and Zhang 2009), telomere dysfunction (Chadeneau *et al.* 1995; Artandi *et al.* 2000; Stewénius *et al.* 2005; Stindl 2008), or centrosome amplification (Fukasawa *et al.* 1996; Lingle *et al.* 1998; Mayer *et al.* 2003; Basto *et al.* 2008; Castellanos *et al.* 2008) starts aneuploidy. Regardless of which mechanism exactly is regarded to lead to aneuploidy, many authors agree that there is some sort of malfunction in chromosomal distribution during mitosis, as described by Hansemann and Boveri already about a 100 years ago. This commentary, however, does not aim to re-examine the aneuploidy versus somatic mutation question, as this has been extensively done by others arguing in favour either of aneuploidy (Duesberg and Rasnick 2000; Duesberg *et al.* 2006; Pathak and Multani 2006; Chi and Jeang 2007) or somatic mutation being the primary cause of cancer (Vogelstein and Kinzler 1993; Bishop 1995; Hahn *et al.* 1999). An important consequence of aneuploidy, no matter how it is established or if it is the ultimate cause of cancer, is genetic instability. This genetic instability drives cancer evolution as well as the evolution of a new species.

4. Cancer as a new species

Although the idea of cancer as a new species has been around since Hansemann's first proposal in 1897, there is not much recent literature addressing this specific topic (Hauser 1903; Huxley 1956; Hauschka 1961; Duesberg and Rasnick 2000; Vincent 2010). In 1956, Huxley stated: 'All autonomous neoplasms can be regarded as the equivalents of new biological species', arguing that 'once the neoplastic process has crossed the threshold of autonomy' it has its 'own specific type of self-replication […] with the capacity for further evolution by the incorporation of suitable mutations' (Huxley 1956). Like Huxley 3 years before, Rous put emphasis on the gap between cancer cells and their ancestors: 'the cells of the most fatal human cancers are far removed from the normal in character' (Rous 1959).

With the HeLa cell line derived from cervix carcinoma cells of Henriette Lacks, probably the best characterized cancer cells have been developing in cell culture for (almost) 60 years. In 1991, Leigh Van Valen and Virginia Maiorana advocated the idea of HeLa cells being an own species: *Helacyton gartleri* of the genus *Helacyton* and the family Helacytidae. The main reasoning of declaring the HeLa cell line as a new species was 'First, their genotype is very different, far outside the range of those of viable humans. Second, they occupy an ecological niche extremely different from that of humans. Third, they persist and expand well beyond the desires of the human cultivators of cells; they are the weeds of cell culture. […] It is […] relevant, that HeLa cells don't exchange genes with real humans' (the HeLa cells have a karyotype with chromosome numbers varying from 43 to 88) (Van Valen 1991). Peter Duesberg argues that the genotypic difference is due to the introduction of aneuploidy and thus 'aneuploidy cells, above all cancer cells, are by definition species of their own that differ from their diploid predecessors in both the number of chromosomes and the dosage of thousands of genes' because 'variation of chromosomes is the basis of speciation' (Duesberg and Rasnick 2000). However, having a closer look at current species definition, cancer cannot be seen as an own independent species. As discussed above, cancer cells do not fulfill the criteria for an independent unicellular asexually reproducing species proposed by Cohan (2002). Due to the notorious instability of the cancer karyotype, cancer cells also lack a strict ancestral-descendant lineage, which does not fit into the meta-population lineage concept proposed by de Queiroz. Therefore, we advance the idea of cancer as a speciation event of a unicellular species.

5. The evolution of a new unicellular species

The question that arises is whether there is an example of a successful evolution of a new unicellular species from a cancer cell if so many speciation events occur. In the vast majority of cases, the evolution of this new species is stopped by the death of the host brought about by the dualistic relationship of the cancer cells towards the host cells.

The view of cancer development and progression as a speciation event is supported by the case of infectious cancers like the canine transmissible venereal tumour (CTVT), which can be passed on from animal to animal (Murgia *et al.* 2006; Rebbeck *et al.* 2009), destructive facial cancer of the Tasmanian Devil (Dingli and Nowak 2006; Pearse and Swift 2006) or transmissible cancer forms in Syrian hamster (Copper *et al.* 1964). This perspective on cancer and on the animal organism is, of course, very problematic. A metazoan, for sure, is not identical with several protozoans only communicating with each other but is located on a totally different branch in the eukaryotic tree of life. We might have to partially accept this point of view, describing the CTVT as 'a cellular parasite that has gained independence from and long outlived its original host' (Murgia *et al.* 2006). Analysing the CTVT carefully, Murgia *et al.* came to the conclusion that all CTVT cells originated from a single cell of a wolf or East Asian breed of dogs 200 to 2500 years ago. Interestingly, the karyotype of CTVT is remarkably constant, despite its aneuploidy (chromosome count varying from 57 to 59; normal dog *Canis familiaris* $2n=78$) (Weber *et al.* 1965; Murray *et al.* 1969; Oshimura *et al.* 1973). Regarding the stabilization of an abnormal karyotype, Murgia draws the connection to long-established human cell lines, like the HeLa cells. This suggests that if a cancer cell, by whatever means, succeeds in evading the deathly dualistic nature of its host, described above, it might finally evolve into a new unicellular species with a stable karyotype.

In 1990, Sen Pathak tried to establish a parallelism between chromosomal alterations in speciation and neoplastic transformation and proposed that the induction of aneuploidy is rather a reaction to environmental stress than an accidental process at arbitrary locations. This has recently been shown in yeast (Dunham *et al.* 2002; Gresham *et al.* 2008), putting forward the idea that a mechanism exist that induces or allows aneuploidy in order to adapt rapidly to a stressful environmental situation. Given a stable environment and good adaption, genetic identity and stability is evolutionary-sensitive. If the environment changes, it makes sense that a mechanism is put in place that allows genetic instability, to adapt within a few generations to the altered situation. The intermittent appearance of phases of evolutionary stability and rapid evolution of new species in the fossil record suggests such a mechanism (Eldredge and Gould 1972). Proposing the idea of 'allowed genetic instability' for the case of cancer would have strong implications on the perception of tumorigenesis and the role of aneuploidy within. For the single cell in a metazoan, if regarded as a compound of potentially independent microbes, the collectivity of cells forms the

environment. When environmental stress is put on the single cell, whether this is through carcinogens, inflammation or nutritive restriction, a process of adaption on the unicellular level might be started. Since this process is on a unicellular level, the evolving clones will compete with its ancestors, turning against them and thus turning against its environment. This idea is very consistent with Virchow's idea 'that the structural composition of a body of considerable size, a so-called individual, always represents a kind of social arrangement of parts, an arrangement of social kind, in which a number of *individual existence* are mutually dependent […]' (Virchow 1863). Following Virchow's analogy of the organism as a democratic 'cell-state', one could see the cancer cell as a criminal living out of society, selfishly destroying and robbing, always finding new ways to hide from the police (immune system), self-replicating (this is of course a problem in the analogy), giving birth to ever more aggressive specimen of his kind. Most of the time they are caught in an early stage, being too naive to slip away from the police surveillance, but very rarely one manages quickly enough to come up with sufficient strategies to survive and develop. As with crime in human societies, cancer arises as a form of survival strategy and as an answer to environmental stress. Criminality is as old as human societies; cancer also exists since the evolution of metazoans.

6. Conclusion

A cell can be affected by several accumulating mutations or permanent stress. Such a pre-damaged cell is additionally affected by another major stress factor. This fundamental event uncouples the cell from the surrounding tissue and further from the organism and leads to the onset of a genetic programme to overcome this stressful situation. It has been shown that the induction of aneuploidy and therefore major genomic changes are effective physiological mechanisms of eukaryotic cells to adapt to these environmental stresses. As seen in cancer cells this aneuploidy changes the characteristics of the cells profoundly, marking the starting point of a process of speciation. In this commentary, we looked at the case of tumour cells in terms of modern species definition to decide whether cancer can be described as a justifiable new species. We came to the conclusion that the obstacles to the cancer as a species thesis (e.g. unstable karyotype) can be overcome if tumorigenisis is seen as the starting point for an ongoing process of speciation on a unicellular level. For the case of CTVT, this process of speciation has been ongoing for about 2000 years, leading to a more or less stable karyotype and a cell species with own characteristics and an ancestral-descendent sequence.

Acknowledgements

We gratefully acknowledge the support of Franziska Miller for editing the English version and critical discussions of this manuscript. We thank Peter Duesberg for inspiring us to do this work and his general advice.

References

Artandi S, Chang S, Lee S, Alson S, Gottlieb G, Chin L and DePinho R 2000 Telomere dysfunction promotes non-reciprocal translocations and epithelial cancers in mice. *Nature* **406** 641–645

Atwood KC, Schneider LK and Ryan FJ 1951 Periodic selection in *Escherichia coli. Proc. Natl. Acad. Sci. USA* **37** 146–155

Bannon JH and Mc Gee MM 2009 Understanding the role of aneuploidy in tumorigenesis. *Biochem. Soc. Trans.* **37** 910–913

Basto R, Brunk K, Vinadogrova T, Peel N, Franz A, Khodjakov A and Raff JW 2008 Centrosome amplification can initiate tumorigenesis in flies. *Cell* **133** 1032–1042

Bishop JM 1995 Cancer: the rise of the genetic paradigm. *Genes Dev.* **9** 1309–1315

Boveri T 1914 *Zur Frage der Entstehung maligner tumoren* (Jena: Gustav Fischer Verlag)

Bozic I, Antal T, Ohtsuki H, Carter H, Kim D, Chen S, Karchin R, Kinzler KW, Vogelstein B and Nowak MA 2010 Accumulation of driver and passenger mutations during tumor progression. *Proc. Natl. Acad. Sci. USA* **107** 18545–18550

Castellanos E, Dominguez P and Gonzalez C 2008 Centrosome dysfunction in Drosophila neural stem cells causes tumors that are not due to genome instability. *Curr. Biol.* **18** 1209–1214

Chadeneau C, Hay K, Hirte H, Gallinger S and Bacchetti S 1995 Telomerase Activity associated with acquisition of malignancy in human colorectal-cancer. *Cancer Res.* **55** 2533–2536

Chi Y-H and Jeang K-T 2007 Aneuploidy and cancer. *J. Cell Biochem.* **102** 531–538

Cohan FM 2001 Bacterial species and speciation. *Syst. Biol.* **50** 513–524

Cohan FM 2002 What are bacterial species? *Annu. Rev. Microbiol.* **56** 457–487

Copper HL, Mackay CM and Banfield WG 1964 Chromosome studies of a contagious reticulum cell sarcoma of the Syrian hamster. *J. Natl. Cancer Inst* .**33** 691–706

de Queiroz K 2005 Ernst Mayr and the modern concept of species. *Proc. Natl. Acad. Sci. USA* **102** Suppl 1 6600–6607

Dingli D and Nowak MA 2006 Cancer biology: infectious tumour cells. *Nature* **443** 35–36

Doolittle WF and Papke RT 2006 Genomics and the bacterial species problem. *Genome Biol.***7** 116

Duesberg P and Rasnick D 2000 Aneuploidy, the somatic mutation that makes cancer a species of its own. *Cell Motil. Cytoskeleton* **47** 81–107

Duesberg P, Fabarius A and Hehlmann R 2004 Aneuploidy, the primary cause of the multilateral genomic instability of neoplastic and preneoplastic cells. *Iubmb Life* **56** 65–81

Duesberg P, Li R, Fabarius A and Hehlmann R 2006 Aneuploidy and cancer: from correlation to causation. *Contrib. Microbiol.* **13** 16–44

Duesberg P, Li R, Rasnick D, Rausch C, Willer A, Rausch C and Hehlmann R 2000 Aneuploidy precedes and segregates with chemical carcinogenesis. *Cancer Genet. Cytogen.* **119** 83–93

Duesberg P, Mandrioli D, McCormack A and Nicholson JM 2011 Is carcinogenesis a form of speciation? *Cell Cycle* **10** 2100–2114

Dunham MJ, Badrane H, Ferea T, Adams J, Brown PO, Rosenzweig F and Botstein D 2002 Characteristic genome rearrangements in experimental evolution of Saccharomyces cerevisiae. *Proc. Natl. Acad. Sci. USA* **99** 16144–16149

Eldredge N and Gould S 1972 Punctuated equilibria: an alternative to phyletic gradualism; in *Models in paleobiology* (ed) TJM Schopf (Freeman, Cooper & Co, San Francisco) pp 82–115

Ferea TL, Botstein D, Brown PO and Rosenzweig RF 1999 Systematic changes in gene expression patterns following adaptive evolution in yeast. *Proc. Natl. Acad. Sci. USA* **96** 9721–9726

Fukasawa K, Choi T, Kuriyama R, Rulong S and Vande Woude GF 1996 Abnormal centrosome amplification in the absence of p53. *Science* **271** 1744–1747

Gartler SM 1968 Apparent Hela cell contamination of human heteroploid cell lines. *Nat. News* **217** 750–751

Goodfellow M, Manfio G and Chun J 1997 Towards a practical species concept for cultivable bacteria; in *Species: The units of biodiversity* (London: Chapman & Hall) pp 25–59

Gresham D, Desai MM, Tucker CM, Jenq HT, Pai DA, Ward A, DeSevo CG, Botstein D and Dunham MJ 2008 The repertoire and dynamics of evolutionary adaptations to controlled nutrient-limited environments in yeast. *PLoS Genet.* **4** e1000303

Hahn WC, Counter CM, Lundberg AS, Beijersbergen RL, Brooks MW and Weinberg RA 1999 Creation of human tumour cells with defined genetic elements. *Nat. News* **400** 464–468

Hanahan D and Weinberg RA 2000 The hallmarks of cancer. *Cell* **100** 57–70

Hansemann D 1897 *Die mikroscopische Diagnose der bösartigen Geschwülste* (Berlin: August Hirschwald)

Hauschka TS 1961 The chromosomes in ontogeny and oncogeny. *Cancer Res.* **21** 957–974

Hauser G 1903 Giebt es eine primaere zur Geschwulstbildung fuehrende Epithelerkrankung? Ein Beitrag zur Geschwulstlehre. *Beitr. Path. Anat. Allg. Path.* **33** 1–31

Heneen WK 1976 HeLa cells and their possible contamination of other cell lines: karyotype studies. *Hereditas* **82** 217–248

Huxley J 1956 Cancer Biology: Comparative and genetic. *Biol. Rev.* **31** 474–513

Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D 2011 Global cancer statistics. *CA Cancer J. Clin.* **61** 69–90

King M 1987 Chromosomal rearrangements, speciation and the theoretical approach. *Heredity* **59** 1–6

Klein A, Li N, Nicholson JM, McCormack AA, Graessmann A and Duesberg P 2010 Transgenic oncogenes induce oncogene-independent cancers with individual karyotypes and phenotypes. *Cancer Genet. Cytogen.* **200** 79–99

Klein A, Wessel R, Graessmann M, Jürgens M, Petersen I, Schmutzler R, Niederacher D, Arnold N, *et al.* 2007 Comparison of gene expression data from human and mouse breast cancers: identification of a conserved breast tumor gene set. *Int. J. Cancer* **121** 683–688

Konstantinidis KT, Ramette A and Tiedje JM 2006 The bacterial species definition in the genomic era. *Philos. Trans. R. Soc. London, B Biol. Sci.* **361** 1929–1940

Kops GJ, Weaver BA and Cleveland DW 2005 On the road to cancer: aneuploidy and the mitotic checkpoint. *Nat. Rev. Cancer* **5** 773–785

Li M and Zhang P 2009 Spindle assembly checkpoint, aneuploidy and tumorigenesis. *Cell Cycle* **8** 3440

Li R, Sonik A, Stindl R, Rasnick D and Duesberg P 2000 Aneuploidy vs. gene mutation hypothesis of cancer: recent study claims mutation but is found to support aneuploidy. *Proc. Natl. Acad. Sci. USA* **97** 3236–3241

Li R, Yerganian G, Duesberg P, Kraemer A, Willer A, Rausch C and Hehlmann R 1997 Aneuploidy correlated 100% with chemical transformation of Chinese hamster cells. *Proc. Natl. Acad. Sci. USA* **94** 14506–14511

Lingle WL, Lutz WH, Ingle JN, Maihle NJ, and Salisbury JL 1998 Centrosome hypertrophy in human breast tumors: implications for genomic stability and cell polarity. *Proc. Natl. Acad. Sci. USA* **95** 2950–2955

Linnaeus C 1767 *Systema naturae* 12th edition (Stockholm: Laurentius Salvius)

Matthey R 1973 The chromosome formulae of eutherian mammals; in *Cytotaxonomy and vertebrate evolution* (eds) AB Chiarelli and E Capanna (New York: Academic Press) pp 531–616

Mayden R 1997 A hierarchy of species concepts: the denouement in the saga of the species problem; in *Species: The units of biodiversity* (eds) MF Claridge, AH Dawah and MR Wilson (London: Chapman & Hall) pp 380–424

Mayer F, Stoop H, Sen S, Bokemeyer C, Oosterhuis JW and Looijenga LH 2003 Aneuploidy of human testicular germ cell tumors is associated with amplification of centrosomes. *Oncogene* **22** 3859–3866

Mayr E 1963 *Animal species and evolution* (Cambridge: Belknap Press/Harvard University Press)

Mayr E 1942 *Systematics and the origin of species* (New York: Harvard University Press)

Merlo L, Pepper J, Reid B and Maley C 2006 Cancer as an evolutionary and ecological process. *Nat. Rev. Cancer* **6** 924–935

Michor F, Iwasa Y, Vogelstein B, Lengauer C and Nowak MA 2005 Can chromosomal instability initiate tumorigenesis? *Semin. Cancer Biol.* **15** 43–49

Murgia C, Pritchard JK, Kim SY, Fassati A and Weiss RA 2006 Clonal origin and evolution of a transmissible cancer. *Cell* **126** 477–487

Murray M, James ZH and Martin WB 1969 A study of the cytology and karyotype of the canine transmissible venereal tumour. *Res. Vet. Sci.* **10** 565–568

Nelson-Rees WA, Hunter L, Darlington GJ and O'Brien SJ 1980 Characteristics of HeLa strains: permanent vs. variable features. *Cytogenet. Cell Genet.* **27** 216–231

Nowell PC 1976 The clonal evolution of tumor cell populations. *Science* **194** 23–28

O'Brien SJ, Menotti-Raymond M, Murphy WJ, Nash WG, Wienberg J, Stanyon R, Copeland NG, Jenkins NA, Womack JE and Marshall Graves JA 1999 The promise of comparative genomics in mammals. *Science* **286** 458–62, 479–81

Oshimura M, Sasaki M, and Makino S 1973 Chromosomal banding patterns in primary and transplanted venereal tumors of the dog. *J. Natl. Cancer Inst.* **51** 1197–1203

Pathak S and Multani AS 2006 Aneuploidy, stem cells and cancer. *EXS* **2006** 49–64

Pathak S 1990 Chromosome alterations in speciation and neoplastic transformation: a parallelism; in *Trends in chromosome research* (ed) T Sharma (New Delhi: Springer Verlag, Narosa Publishing House) pp 204–220

Pearse A-M and Swift K 2006 Allograft theory: transmission of devil facial-tumour disease. *Nature* **439** 549

Pihan G and Doxsey SJ 2003 Mutations and aneuploidy: co-conspirators in cancer? *Cancer Cell* **4** 89–94

Rebbeck CA, Thomas R, Breen M, Leroi AM and Burt A 2009 Origins and evolution of a transmissible cancer. *Evolution* **63** 2340–2349

Rokas A 2008 The origins of multicellularity and the early history of the genetic toolkit for animal development. *Annu. Rev. Genet.* **42** 235–251

Rous P 1959 Surmise and fact on the nature of cancer. *Nature* **183** 1357–1361

Rubin LL and de Sauvage FJ 2006 Targeting the Hedgehog pathway in cancer. *Nat. Rev. Drug Discovery* **5** 1026–1033

Schneider BL and Kulesz-Martin M 2004 Destructive cycles: the role of genomic instability and adaptation in carcinogenesis. *Carcinogenesis* **25** 2033–2044

Stackebrandt E and Goebel B 1994 Taxonomic note: a place for DNA-DNA reassociation and 16S rRNA sequence analysis in the present species definition in bacteriology. *Int. J. Syst. Bacteriol.* **44** 846–849

Steinberg D 2004 Appraising aneuploidy as a cancer cause - A conference considers a theory that blames tumorigenesis on chromosomal gains and losses. *Scientist* **18** 26–27

Stemmler MP 2008 Cadherins in development and cancer. *Mol. Biosyst.* **4** 835–850

Stewénius Y, Gorunova L, Jonson T, Larsson N, Höglund M, Mandahl N, Mertens F, Mitelman F and Gisselsson D 2005 Structural and numerical chromosome changes in colon cancer develop through telomere-mediated anaphase bridges, not through mitotic multipolarity. *Proc. Natl. Acad. Sci. USA* **102** 5541–5546

Stindl R 2008 Defining the steps that lead to cancer: replicative telomere erosion, aneuploidy and an epigenetic maturation arrest of tissue stem cells. *Med. Hypotheses* **71** 126–140

Storchova Z and Pellman D 2004 From polyploidy to aneuploidy, genome instability and cancer. *Nat. Rev. Mol. Cell Biol*. **5** 45–54

Templeton A 1989 The meaning of species and speciation: a genetic perspective; in *Speciation and its consequences* (eds) D Otte and JA Endler (Sunderland, MA: Sinauer Associates, Inc) pp 3–27

The World Health Organization 2008 *The global burden of disease: 2004 update* (Geneva: The World Health Organization)

Van Valen L 1991 HeLa, a new microbial species. *Evolutionary Theory* **10** 71–74

Vincent MD 2010 The animal within: carcinogenesis and the clonal evolution of cancer cells are speciation events sensu stricto. *Evolution* **64** 1173–1183

Virchow R 1863 *Cellular pathology as based upon physiological and pathological histology, 20 Lectures delivered in the Pathological Institute of Berlin, during the months of February, March and April 1858* (Philadelphia: JB Lippincott and Co)

Virchow R 1859 *Die Cellularpathologie in Ihrer Begründung Auf Physiologische und Pathologische Gewebelehre* 2nd edition (Berlin: Verlag von August Hirschwald)

Vogelstein B and Kinzler KW 1993 The multistep nature of cancer. *Trends Genet.* **9** 138–141

Wayne L, Brenner D, Colwell R, Grimont PAD, Kandler O, Krichevsky MI, Moore LH, Moore WEC, *et al.* 1987 Report of the ad-hoc-committee on reconciliation of approaches to bacterial systematics. *Int. J. Syst. Bacteriol.* **37** 463–464

Weber WT, Nowell PC and Hare WC 1965 Chromosome studies of a transplanted and a primary canine venereal sarcoma. *J. Natl. Cancer Inst.* **35** 537–547

White MJD 1978 *Modes of speciation* (San Francisco: WH Freeman and Co)

Yosida TH 1973 Evolution of karyotypes and differentiation in 13 Rattus species. *Chromosoma* **40** 285–297

Yosida TH 1983 Karyotype evolution and tumor development. *Cancer Genet. Cytogen.* **8** 153–179

Samuel Knauss and Andreas Klein*
Institute of Biochemistry, Charité – Universitätsmedizin Berlin
Campus Virchow Klinikum,
Oudenarder Str. 16-20, 13347 Berlin, Germany
**Corresponding author (andreas.klein@charite.de)*