Review Article

Phylogeny, Regeneration, Ageing and Cancer: Role of Microenvironment and Possibility of Its Therapeutic Manipulation

(evolution / regeneration / ageing / cancer / tumour microenvironment)

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Abstract. Data about the possible correlation between reduction of the regeneration capacity in the course of phylogeny and formation of malignant tumours have been summarized from invertebrates to mammals. The evolutionarily increasing complexity of body building plane and expectancy of longevity in the course of phylogeny seems to be grossly negatively correlated with diminished regeneration capacity, but positively with increased occurrence of malignant tumours. A certain evolution-based switch-off mechanism reducing the extent of regeneration in developmentally complicated and long-living animals such as mammals and birds can be hypothesized and benefits of loss of this ability are discussed. This high incidence of malignancies seems to be related, in addition to other factors, to prolonged and cumulative exposure to cancerogenic stimuli in the course of lifetime. Longevity, supported by the progress and availability of medical care to the population, has been unveiling this phenomenon during recent decades. From this point of view, ageing represents the main risk for cancer acquisition. The probable role of microenvironment in all the discussed phenomena such as healing/regeneration, inflammation, and cancer is discussed and targeting of microenvironment is consequently predicted as a possible therapeutic target where controlled manipulation may represent a new approach to the treatment of cancer patients.

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Abbreviations: CAFs – cancer-associated fibroblasts, ECM – extracellular matrix, EMT – epithelial to mesenchymal transition.

Regeneration in the course of evolution

Regeneration represents a complex sequence of cellular and molecular events ideally resulting in complete restoration of the damaged part of the body or tissues, including their complete functions. The extent and efficiency of regeneration is variable and includes regeneration (i) of a significant extent of the body (seen e.g. in platyhelminthes), (ii) of highly complex structures (for example limb of newts), (iii) of internal organs (for example liver), (iv) of tissues (epidermis) and (v) of cells (axons of neurons). The last three examples occurred in many animals, including humans as representatives of higher vertebrates (Bely and Nyberg, 2009). The ability of regeneration of almost the whole body is evolutionarily restricted to the members of invertebrates and very few chordates (urochordates). The most studied model organisms here are flatworms – platyhelminthes (Elliot and Sánchez Alvarado, 2013). Surprisingly, the comparable phylogenetic level is not always associated with identical extent of regenerative efficiency, and poorly regenerative flatworms are known. Invertebrates capable of regenerating the whole body have usually preserved the ability of asexual reproduction (van Bekkum, 2004). Shortly, evolutional advantages of asexual and sexual reproductive modes are the low cost of reproduction and the increase in genetic diversity, respectively. Because transmission of genetic information to the next generation is directly linked to the species survival, reproductive success or failure is crucial for all species. Therefore, the mechanism underlying reproductive strategy regulation is a fundamental principle underpinning the continuation, evolution, and diversity of organisms (Nodono et al., 2012).

It is already widely accepted in evolutionary biology that the presence of a coevolving pathogen selects populations for and maintains high levels of out-crossing and

therefore arising genetic variability of offspring; however, the cost of reproduction is somewhat higher (Morran et al., 2011). Thus it seems not surprising that semelparous flatworms (e.g. *Procotyla fluviatilis*) with pronounced strategy of sexual reproduction are deficient in regeneration. Mechanisms responsible for this evolutionary strategic failure of regeneration were identified by next-generation sequencing (Sikes and Newmark, 2013).

The ability to regenerate complex structures is preserved even in vertebrates such as amphibians, and in case of tail in some species of lizards (reptiles) or complex regeneration of fin as in teleost fish (Nachtrab et al., 2013). It is of note that the regeneration of fingertips that meets the condition of regeneration of complex structure has also been very rarely reported in human child (Vidal and Dickson, 1993; Wicker and Kamler, 2009); however, due to sporadic incidence the underlying mechanisms are only poorly understood in humans. On the contrary, consequences of the so-called amniotic band syndrome, leading sometimes to even prenatal auto-amputations or irreversible functional and structural changes, are reported with higher frequency in the literature (Richter et al., 2012). Even here the pathogenesis also remains elusive.

Regeneration of only a limited number of complex organs such as liver and many tissues such as epidermis or bone is very common in all mammals. The postnatal healing of wounds is in humans frequently connected with scarification as a result of incomplete regeneration. Interestingly, the prenatal healing is scar-less, where the main differences between the adult and foetal healing is based on lower extent of inflammation and lower and more controlled production of extracellular matrix in the wounded foetuses (Larson et al., 2010). It seems that foetal healing continues even in the course of first postnatal days (Borský et al., 2007). The process of regeneration seems to be also influenced in vertebrates, in addition to other factors, by the length of telomeres and telomerase activity (Cronkhite et al., 2008; Lund et al., 2009; Anchelin et al., 2011; von Figura et al., 2011). It is generally accepted that telomere shortening is age-dependent, but it should be noted here that the length of telomeres may not be directly related to the calendar age of the subject (Boonekamp et al., 2013; Sanders and Newman, 2013). Summarizing these data, the extent of regeneration seems to be inversely correlated with the position of animal species in the phylogeny, where the complex structure of body building plane in higher vertebrates such as mammals or birds, conditioned by extremely complicated ontogeny, can bring about serious errors during the regeneration. Therefore, the extent of regeneration in these organisms seems to be reduced.

Malignant tumours in evolution

The available sum of data about the incidence of malignant tumours in invertebrates is very limited. It seems that spontaneous tumours in these species (including flatworms and annelids capable of extensive regeneration) are very rare (Lange, 1966; Robert, 2010). The lesions with appearance of malignant tumours can be induced experimentally in flatworms such as *Dugesia dorotocephala* by exposure to carcinogens present in the environment where the animals are kept (Foster, 1963; Hall et al., 1986). However, even after prolonged exposure to cancerogenic substances the number of affected animals is not very high. Despite its rarity, the occurrence of malignancies in these plathyhelminthes is very important, because it depicts that even these phylogenetically simple well-regenerating animals possess evolutionarily conserved genes and pathways necessary for the malignant tumour development. Furthermore, it is very important that flatworms with a limited extent of regenerative potential display different reactions to chemical cancerogens depending on the site of application. The anterior segment of their body is more resistant to cancerogenic effects compared to the posterior half, which exhibits only a limited extent of regeneration (Oviedo and Beane, 2009). This phenomenon of imperfect regeneration seems to be dependent on aberrant Wnt signalling in non-regenerating parts of the worm (Almuedo-Castillo et al., 2012; Liu et al., 2013; Sikes and Newmark, 2013). Not surprisingly, the crucial role of Wnt signalling in cancer formation and regeneration has been well documented. This signalling pathway thus seems to be a possible link between both biological processes, cancer and regeneration (Ouyang et al., 2013).

The incidence of malignant tumours in vertebrates has been far better studied and documented. The fish suffer from many types of tumours. These tumours are frequently induced by the same mechanisms as in humans (Amattruda and Patton, 2008). Zebrafish thus rightfully represents an excellent model for experimental oncology. Tumours in zebrafish can be triggered by various agents including retroviruses (Coffee et al., 2013) and environmental pollution by cancerogens (Baumann, 1992; Pikney et al., 2011) and many other causes (Liu and Leach, 2011). The fish of genus *Xiphophorus* frequently suffer from spontaneously developing melanoma, namely in the elderly (Ozato and Wakamatsu, 1981). Data about the natural incidence of tumours in fish are sparse, but it seems that the natural occurrence of malignancies is significantly lower than in the mammals (Groff, 2004). Amphibians are also able to develop tumours spontaneously (Asashima et al., 1982). Interestingly, in the context of this article, Urodeles with higher regeneration activity have lower incidence of malignancies than Anura (Anver, 1992; Roy and Gatien, 2008). It was reported that application of chemical cancerogens to regenerative blastema of limbs in Urodeles results in formation of tumours with low frequency, lower than could be expected of e.g. mammals. In this context, the cancerogenic agents intraperitoneally applied to the newt have a strong teratogenic effect on the regenerating limb (Pfeiffer et al., 1985; Brockers, 1998).

In mammals, namely in humans, tumours are frequent and they represent a serious medical problem. Ma-

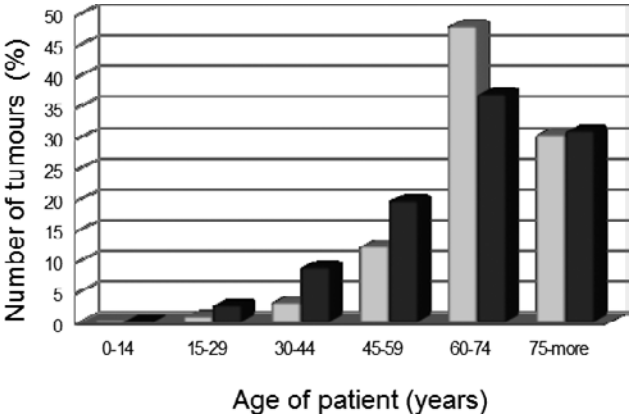

Fig. 1. Incidence of malignant neoplasms in the Czech Republic in dependence on the age of patients in the course of 2010. Graph was constructed from the data published in Zvolský (2013). Light gray columns represent males and the dark gray ones indicate females.

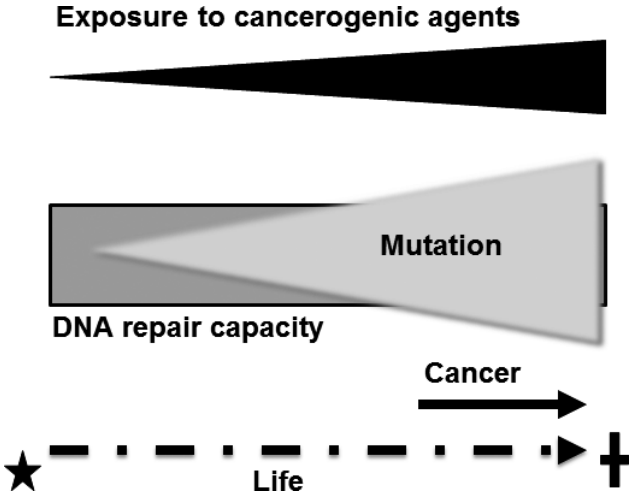

Fig. 2. Long-term exposure to cancerogenic agents seems to be responsible for accumulation of mutations over the capacity of DNA-reparation mechanism. This moment seems to be important for cancer formation.

lignancies occurring during the foetal period are very rare (Sebire and Jauniaux, 2009). They are usually associated with serious genetic alterations, and therefore the affected embryos/foetuses as candidates for cancer formation are usually aborted. The incidence of tumours increases with age. Tumours are relatively rare in the childhood and frequent above 60 years of age in dependence on the type of malignancy (Fig. 1) (Hoffe and Balducci, 2012; Zvolský, 2013). This increased incidence in the elderly can be attributed to the significantly increased survival of humans in the last decades based on the progress of medical technologies (e.g. antibiotics, balloon angioplasty) and general accessibility of medical care. The longevity also brings about prolonged exposure to genotoxic agents such as various chemicals and irradiation, frequently with cumulative effects, which was observed namely as a stochastic effect of low-dose long-term irradiation. Theoretically, these agents cause DNA defects, and when the sum exceeds the capacity of DNA repair, apoptosis is triggered. If the seriously damaged cells survive, they can cause cancer (Jackson and Bartek, 2009; Cha and Yim, 2013; Kleiblova et al., 2013) (Fig. 2). This process of elimination failure seems to be especially important in stem cells, leading to stem cell genetic instability that can be significant for cancer formation (Kenyon and Gerson, 2007). The reduced DNA repair efficiency can be associated with increased cancer incidence (Thamm et al., 2013). The relationship of age, DNA repair mechanism and cancer is clearly visible in the course of premature ageing (Dianov, 2011; Niedernhofer et al., 2011; Kanagaraj et al., 2012; Suman et al., 2013). This hypothesis is supported by the low incidence of cancer formation in patients suffering from Huntington disease, where the DNA repair mechanism is accelerated in comparison with normal population (Sørensen et al., 1999). However, this explanation might seem to be mechanistic. It is also necessary to include the changes in the aged organism, frequently associated with altered regulations (immune, endocrine, neurologic) resulting in metabolic disorders, to interpret the cancer accumulation in the age above 60 (Kim nad Sharpless, 2006; Rossi et al., 2008; Anisimov et al., 2009; Thompson et al., 2013).

Similarity between regeneration and cancer: causality or coincidental phenomenon

Both processes involve cells with properties of stem cells

As demonstrated above, regeneration and cancer occurrence seem to be developmentally controlled with inverted mutual correlation. The whole body regeneration in flatworms needs the activity of a population of so-called neoblasts, representing cells with the properties of stem cells (Aboobaker, 2011; Slack, 2011). Regeneration of complex structures of amphibian limb or fish fin is also associated with formation of blastema composed of cells of low differentiation status. The participation of pre-existing stem cells in the blastema formation is not clear. It seems that part of blastema cells are formed by the process of dedifferentiation, and some of them therefore subsequently acquire the properties of stem cells (Kawakami, 2010; Tamura et al., 2010). Association between cancer and regeneration was also hypothesized by Pomerantz and Blau (2013), who demonstrated participation of tumour suppressor genes in the control of tissue regeneration. The role of multipotent adult tissue stem cells in the self-renewal and tissue healing in all mammals including humans has been well documented. The flatworm stem cells – neoblasts – must be highly pluripotent because these cells are able to recover all cell types in the regenerating animal (Sánchez Alvarado, 2012). The cells with a high level of pluripotency are also present in the human bone marrow, as is

evident from the therapeutic application of bone marrow grafting in clinical medicine. Already iconic became the evidence of female hosts with no history of bearing male child who received the therapeutic bone marrow graft of male origin and many of their tissues consequently exhibited clear microchimerism (Ramakrishnan et al., 2006). However, participation of bone marrow haematopoietic stem cells in extensive regeneration in humans is not clinically relevant.

The stem cells controlled by the developmental/regeneration-specific signalling pathways seem to also be very important for formation of malignant tumours (Pearson and Sánchez Alvarado, 2010). So-called cancer stem cells participate in the establishment of tumour tissue and in cancer spreading in the organism. However, the origin of these cells is not fully understood and it is not clear whether these cells are behind the formation of all types of tumours. These cancer stem cells can be formed by mutations of normal tissue stem cells. However, other observations indicated that the differentiated cells can acquire properties of stem cells after several multistep mutations typical of cancer cells (Reya et al., 2001; Trosko, 2008, 2009; McDonald et al., 2009; Sell, 2010). Normal adult tissue stem cells have unique properties. Their proliferation is usually very slow. Stem cells divide under the physiological conditions by asymmetric mitosis, where only one of the daughter cells has again the properties of the stem cell. The other one, so-called transit amplifying cell (starting element of the differentiation cascade), is proliferating rapidly but with restricted number of divisions. The functional definition of stemness was also based on the ability of cells (here termed "side population") to actively exclude xenobiotics from their cytoplasm to prevent damage to the genetic information (Lou and Dean, 2007). The described properties of normal stem cells seem to also be present in cancer stem cells, where they can be behind such serious complications of cancer therapy as multidrug resistance resulting in minimal residual disease (Motlík et al., 2007; Gil et al., 2008). These data urge for therapeutic targeting of cancer stem cells to effectively treat the tumours (Reya et al., 2001; Motlík et al., 2007). Unfortunately, this is still a great challenge without any recent practical options at this state of the art (Zhao et al., 2012).

As was shown above, both regeneration and cancer are dependent on the stem cell population. The very suggestive connection between both phenomena has been demonstrated in amphibians, where amputation of a limb in the vicinity of cancer can cure the disease through the process of regeneration (Oviedo and Beane, 2009). This observation presents a good parallel to the results demonstrating a similar effect of embryonic microenvironment on various cancer cell type behaviours, including aggressive melanoma. The embryonic microenvironment abrogates malignant behaviour of melanoma cells after grafting and malignant cells acquire the potential of neural crest stem cells (Postovit et al., 2008) or exhibit differentiation markers when they are cultured in the medium conditioned by products of embryonic stem cells or by embryonic extract (Kodet et al., 2013).

Necessity of permissive microenvironment

It is a textbook knowledge that stem cells need a highly specific microenvironment also called the niche. It is necessary for their correct function and maintenance of cell stemness. Because the features of the microenvironment such as cell types, extracellular matrix molecules, or cytokine network required have not yet been well characterized for the majority of tissue stem cells, *in vitro* production of stem cells for regenerative medicine in a clinically relevant volume is not yet possible. Wound healing/regeneration is dependent on well-orchestrated sequential events. This tight regulation includes the timely presence of distinct cell types in the regeneration site. This is very similar to the data received on tumour stroma (Plzák et al., 2010). The microenvironment of either tumours or wound bed is infiltrated by inflammatory cells removing tissue debris and producing a wide panel of cytokines. Tumour stroma as well as wound bed also contain activated fibroblasts/myofibroblasts, which produce molecules of extracellular matrix, various cytokines and in the case of wound healing participate in the wound contraction (Fig. 3A-C).

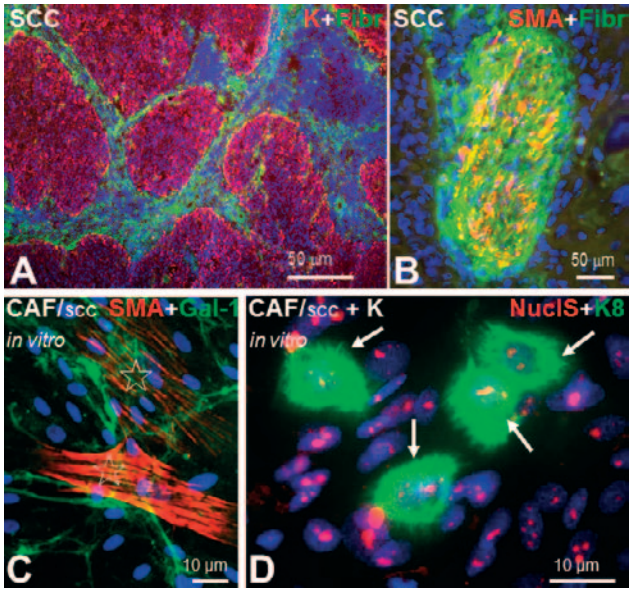

Fig. 3. Detection of fibronectin (Fibr, green signal) in the stroma of squamous cell carcinoma (SCC) of oral cavity. The cancer cells express keratin (red signal) (A). Many fibroblasts in the stroma of SCC (oral cavity) exhibit smooth muscle actin (SMA, red signal) (B). Fibroblasts isolated from SCC of oral cavity exhibit SMA (red signal, asterisk) as a typical feature of cancer-associated fibroblasts (CAF). Galectin-1 (Gal-1) produced by these cells is marked in green (C). CAFs isolated from SCC of oral cavity induced expression of type 8 keratin (green signal) in co-cultured normal human keratinocytes (K, arrow). Nucleoli of both CAFs and keratinocytes express a marker of non-matured cells – nucleostemin (NuclS, red signal) (B).

The complexity of structure and functions of tumour stroma represents a very important limiting condition for tumour spreading through the organism (Mareel and Constantino, 2011). The stroma and wound bed reaction, respectively, are necessary for the growth of capillaries and also for the stimulation of proliferation of epithelial cells and their migration. The similarity between cancer and wound healing has been well highlighted by Harvard University pathologist Harold Dvorak (1986) and the data about the mentioned similarity are summarized in Table 1. It is possible to conclude that remarkable similarities between both mentioned situations do exist, but the tumour compared to an acute wound is a never-ending story and apart from similarities, significant differences are also evident. The relationship of chronic wounds and cancer has been known at least since the description of so-called Marjolins ulcer in 19th century. Deciphering the molecular mechanism in chronic non-healing wounds seems to be more complicated due to their heterogeneity, lack of appropriated models, and frequently also due to loose definitions. Dissecting chronic inflammation from cancerogenesis in clinical samples is usually impossible. Hereby the Dvorak's parallel that "cancer is a wound that never heals" becomes even more relevant.

Inflammatory reaction in cancer

The cells of the immune system also actively infiltrate the site of tumour similarly to most normal tissues to achieve immunological surveillance. Inflammatory cells might thus reflect the adverse reaction of the immune system against cancer cells. On the other hand, similarly to the wound healing/regeneration, the immune cells can stimulate growth of various cells including cancer cells by production of bioactive substances such as pro-inflammatory cytokines, chemokines, prostaglandins and others (Kundu and Surh, 2008). Some data also suggest that inflammatory cells are able to influence the cancer cell to spread in the organism and form metastases (Wu and Zhou, 2009).

Recently, various new methods and strategies of cancer immunotherapy have been tested. The therapy of prostate cancer by dendritic cells capable of activating the immune system with consequent destruction of cancer cells by T cells represents a good example of this therapeutic effort (Rozková et al., 2009). On the other hand, the strategy of anti-CTLA immunotherapy in melanoma starts with suppression of the function of a certain subset of T cells (Hanaizi et al., 2012). The physiological changes associated with ageing of the immune system may have some relation to the elevated incidence of tumours in the population over 60 (Bukovsky et al., 2009). The stimulating effect of chronic, frequently sterile inflammation such as so-called inflammatory pro-cancerogenic microeinvironment on cancer formation has been well demonstrated by the positive influence on non-steroid anti-rheumatic drugs as cancer-preventing agents (Greenberg and Baron, 1996).

Cancer-associated fibroblasts

Cancer-associated fibroblasts (CAFs) represent the principal cell type of cancer stroma. CAFs frequently express smooth muscle α-actin (Fig. 3B, C). However, this marker cannot fully and exclusively define the cell type. Cells with very similar properties are also present in granulation tissue, where they facilitate the wound contraction, and are traditionally called myofibroblasts. Their formation from normal local fibroblasts and probably also from other cell types including cancer cells is induced in the context of pathological situation by TGF-β1 (Lewis et al., 2004; De Wever et al., 2008), probably in cooperation with other co-stimulatory substances such as galectin-1 (Dvořánková et al., 2011). It is of note that fibroblasts probably arising from different sources can be employed at one site, as it is evident from samples of kidney fibrosis. Fibroblasts are here also very similar to CAFs (Lebleu et al., 2013). It is still questionable whether CAFs represent a distinguished cell type. Is seems to be more probable that CAFs represent a functional status (Madar et al., 2013). On the other hand, CAF transcriptome is significantly different from normal fibroblasts at the whole genome level, where they differ in the expression of almost 600 genes (Strnad et al., 2010). CAFs produce molecules of extracellular matrix very similar to those produced in the course of wound healing, including tenascin, fibronectin and galectin-1 (Klíma et., al., 2009; Brellier and Chiquet-Ehrismann, 2012; Valach et al., 2012).

Table 1. Comparison of wound healing and cancer

Event	Wound		Cancer	
	Presence	Duration	Presence	Duration
Inflammation:				
1) Resorption of cell and extracellular matrix debris	Yes	Transient	Yes	Permanent
2) Extracellular matrix remodelling	Yes	Transient	Yes	Permanent
3) Production of bioactive cytokines	Yes	Transient	Yes	Permanent
Fibroblasts:				
1) Activation, remodelling of extracellular matrix, production of bioactive cytokines	Yes	Transient	Yes	Permanent
2) Transition to myofibroblasts	Yes	Transient	Yes	Permanent
Epithelium:				
1) Hyperproliferation	Yes	Transient	Yes	Permanent
2) Epithelial to mesenchymal transition	Yes	Transient	Yes	Permanent

The naked mole-rat is an extremely long-living rodent with documented survival exceeding 28 years. Surprisingly, this longevity is associated with a very low incidence of tumours (Buffenstein, 2005). The importance of extracellular matrix (ECM) produced by fibroblasts can be behind this phenomenon owing to certain unique features of ECM in these animals. High-molecular-mass hyaluronan produced by fibroblasts in high quantity in these animals seems to be crucial for their resistance to cancer (Tian et al., 2013).

CAFs also produce other bioactive substances participating in the control of inflammation (IL-6, IL-8, CXCL-1) that are also present in the course of wound healing. Receptors for these factors are also expressed by the epithelial cells (Kolář et al., 2012). Comparing production of IL-6, IL-8, CXCL-1 by normal fibroblasts and CAFs after stimulation by cancer cells, the production is sustained in the case of CAFs and only transitory in the case of normal fibroblasts (Szabo et al., 2013). It is of note that CAFs are able to stimulate the low differentiation status of epithelial cells. The stem cell-like inducing features of CAFs can thus be important for the wound healing/regeneration and cancer growth (Fig. 2D) (Lacina et al., 2007; Szabo et al. 2011). CAFs prepared from squamous cell carcinoma strongly induce *in vitro* transition of normal keratinocytes to mesenchymal phenotype (Lacina et al., 2007) and a similar effect has been observed in breast cancer (Lebret et al., 2007). This process is associated with loss of typical intercellular contacts and switch of expression of keratin intermediate filaments to vimentin. Epithelial to mesenchymal transition (EMT) is also a phenomenon connecting the prenatal development, healing and cancerogenesis (Thierry and Lim, 2013). EMT is present in the course of morphogenesis of e.g. embryonic neural crest. Wound healing also requires migration of epithelial cells acquiring some features of mesenchymal cells from the wound edge to the centre. In tumours EMT represents a crucial feature because, as is generally known, it facilitates the migratory potential of cancer cells and so improves their metastatic potential (Savagner et al., 2005; Micalizzi and Ford, 2009; Plzák et al., 2010). Of note, mesenchymal cells arising from EMT frequently also acquire properties similar to stem cells (Asli and Harvey, 2013). In general, the biological activity of CAFs seems to be independent of the type of tissue from which the tumour has originated (Dvořánková et al., 2012). Data from the chronic age-related disorders such as chronic leg ulcers demonstrated molecular differences between "old" and "young" fibroblasts (Wall et al., 2008). Perhaps these differences can also be behind the elevated incidence of tumours (e.g. cutaneous squamous cell carcinomas) in senior age as hypothesized recently (Travers et al., 2013). These data demonstrate the significant role of fibroblasts and their functional states as architects of tumour growth and progression (Marsh et al., 2013).

Perspectives and therapeutic consequences

Data summarized in this article demonstrate that the ability of extensive regeneration ranging from large parts of the whole body to whole limbs/organs is dependent on the position of the particular animal species in phylogeny. The presented data demonstrate the presence of hypothetical mechanisms that are able to switch off the extensive regeneration potential. We also have to address the question what evolutionary benefits are achieved in this way. We may also hypothesize that the ability of nearly subtotal body regeneration is seen predominantly in the organisms with ability of asexual reproduction, as was shown in certain flatworms. The loss of regenerative potential might be compensated by evolutionarily advantageous increased variability of offspring due to random mixing of maternal and paternal alleles. Intriguingly, exceptional species highly contrasting with close relatives by surprisingly low or high regenerative potential are found either in flatworms or in mammals (Seifert et al., 2012). Reduction of the regenerative potential may thus have some consequences in the high incidence of malignancies in the organisms with complicated complex body building plane developed during evolution and requiring longevity (as seen in humans). However, the integrity of genetic information is well guided, and the control mechanisms seem to be unable to compensate for all the frequently occurring errors acquired during genetic information processing in the long course of lifetime. Moreover, it seems that the gene reparative potential in humans is decreasing during ageing (Roy and Gatien, 2008). The population ageing may therefore be considered as the main risk factor for malignant disease in humans in the majority of countries over the world (Fig. 4).

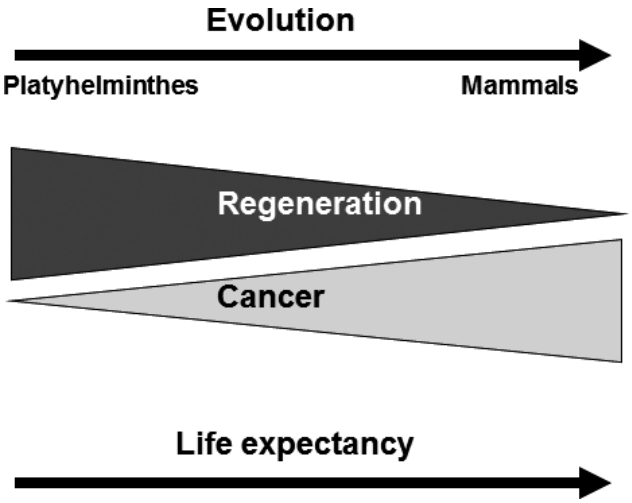

Fig. 4. Diagram demonstrating relations between the position of the organism in evolution, regenerative potential, frequency of tumour formation, and perspective of longevity.

It is hypothesized that bypassing telomere shortening by proliferating cells under specific genetic/epigenetic conditions may result in genomic instability and cancer formation (Shay and Wright, 2011). Therefore, the control of the telomere length should be close to this developmentally based switch-off mechanism. This theory might be supported by recently published observation of telomere length regulation in planarians, where asexual reproduction is associated with stable telomere length, but the sexual mode of reproduction is associated with telomere erosion similarly to evolutionarily higher species (Tasaka et al., 2013). The therapeutic manipulation of telomere length could be very promising for therapy of human tumours (Sprouse et al., 2012). Some therapeutic effect can also be expected from the manipulation of microenvironment, because as demonstrated above, both inflammatory cells and CAFs are important for formation of permissive microenvironment supporting the regeneration/healing and cancer progression, respectively. CAFs and inflammatory cells produce many bioactive substances ranging from extracellular matrix to cytokines. These factors are able to influence the biological behaviour of cancer, including metastasizing. The therapeutic targeting of cancer stroma can thus be a useful therapeutic tool to influence the biological behaviour of tumour. Numerous drugs including antibodies targeted against receptors, molecules of extracellular matrix and cytokines were prepared and even clinically tested to influence the cancer cell-stroma crosstalk (Hofmeister et al., 2008; Zhang and Liu, 2013), with slightly encouraging results. The molecular communication between cancer cells and stroma is represented by a highly complex network of molecular interactions. Targeting of only one molecule and its pathway seems to be frequently therapeutically insufficient and the alteration of more targets seems to be necessary (Kolář et al., 2012). Moreover, one stromal molecule, for example galectin-1, can exhibit both cancer-suppressing and cancer-stimulating effects. Galectin-1 reduces the anti-tumour immune response and stimulates formation of CAFs, supporting the tumour growth and metastasizing. On the other hand, the same molecule is able to interact with integrin receptors and so stimulate the apoptosis of cancer cells (Smetana et al., 2013).

Data presented in this article encourage the notion that the therapeutic manipulation of tumour stroma should be a new paradigm of personalized anticancer therapy (De Palma and Hanahan, 2012). Affecting the non-malignant components of tumour microenvironment by therapy may influence the biological properties of the malignant cell population. However promising is the recent progress in stroma targeting, more precise insight into the cancer cell-stroma interaction is required.

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