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Evolutionary karyotypic theory of cancer *versus* conventional cancer gene mutation theory

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For decades the conventional gene mutation cancer theory has been postulating that cancer is a genetic disease considered as a result of deterministic sequential accumulation of mutations in the handful of «driver» cancer genes occurring in a continuous linear pattern of cancer progression. However, in contrast to this postulate, recent whole genome and exome sequencing studies of primary tumor bulk and metastases or separate regions withing the same sample have revealed a large number of stochastic gene mutations for each individual with the same cancer type and significant intratumoral genetic heterogeneity with «branched evolutionary tumor growth» or «punctuated clonal evolution without observable intermediate branching» or «no dominant clones in the cancer tissue». Meanwhile, the stochastic karyotypic variation and intratumor heterogeneity are recognized to be the driving force of tumor evolution and major factors in determining relapse with acquired drug resistance. The karyotype evolution/chromosome instability and the resulting magnitude of intratumor heterogeneity significantly correlate with tumorigenic potential of cells, tumor disease progression from precancerous lesions to malignant tumors and metastases, correlate with patient survival, treatment sensitivity, and the risk of acquired resistance. Here, we discuss importance of the evolutionary karyotypic theory in understanding the cancer biology and mechanisms of tumor drug resistance.

Keywords: tumor evolution, karyotype, chromosome instability, intratumor heterogeneity, cancer gene, drug resistance.

Introduction. Evidence of tumors has been recorded from molluscs to mammals [1]. There is no correlation between body size, longevity and cancer across species (Peto's paradox), with cancer rates varing twofold, whereas the difference of mammals size reaching a million-fold variation. However, cancer occurs at astonishingly high rates and can be responsible for 20–46 % of total deaths in animals [2]. Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries [3]. Thus, it is justified the increasing financing of tumor biology investigations with especial emphasis on treatment. Nevertheless, as it is stated, «since former US President Richard Nixon declared the «War on Cancer» almost 40 years ago, little progress has been made on reducing the lifetime risk of cancer and increasing survival rates for patients with late-stage diagnoses» [2]. There is an opinion that «public health initiatives, the introduction of national screening programmes, refinements in operative strategy, reductions in operative mortality and advances in the detection of early cancers, rather than an increase in the efficacy of current anticancer agents, has resulted in the improved survival rates seen in certain solid tumour subtypes» [4]. Indeed, multiple diverse clinic trials have failed to demonstrate effective curable chemotherapy [5–22]. What is the reason for failure?

Evolutionary karyotypic cancer theory. Nowadays, almost all treatment strategies are based on the conventional cancer gene mutation theory, which was postulating for decades that cancer is a genetic disease being considered as a result of deterministic sequential accumulation of mutations in the handful of «driver» cancer genes occurring in a continuous linear pattern of cancer progression [23–28]. However, the recent whole genome and exome sequencing studies of tumor bulk revea-

led a large number of stochastic gene mutations for each individual with the same cancer type [29–34]. For example, 2576 somatic mutations were identified across 1507 coding genes from 441 tumors comprising breast, lung, ovarian, and prostate cancer types and subtypes [35]. The Network of Cancer Genes (NCG 3.0, http://bio.ifom-ieo-campus.it/ncg) have collected information on 1494 cancer genes found mutated in 16 different cancer types [33]. The census of cancer genes (http://www.sanger.ac.uk/genetics/CGP/Census/) includes 487 mutated genes (data on March 2012) manually curated from the scientific literature, which are proved to induce or accelerate cancer development being appropriately changed (point mutations, deletions, translocations or amplifications) (criteria for inclusion in the census of cancer genes are considered in [36]). Meanwhile, the whole exome sequencing of multiple spatially separated samples obtained from the same tumor and metastases followed by phylogenetic reconstruction of tumor progression has revealed significant intratumoral genetic heterogeneity with «no dominant clones in the cancer tissue» [37] or «punctuated clonal evolution … without observable intermediate branching» [38] or «branched evolutionary tumor growth» with 63 to 69 % of all somatic mutations not detectable across every tumor region and some genes undergoing multiple distinct and spatially separated inactivating mutations within a single tumor [39]. Studies on chronic lymphocytic leukemia have demonstrated that tumor progression can occur in «either a linear or branching manner, with multiple genetic subclones evolving either in succession or in parallel» [40, 41]. Evaluation of the clonal relationships among pancreatic cancer metastases and primary tumor has led to conclusion that the genetic heterogeneity of metastases reflects heterogeneity already existing within the primary carcinoma, and that the primary carcinoma is a mixture of numerous subclones [42]. Multiregional exome sequencing of prostate cancer has shown the presence of somatically independent tumors within the same prostate [43]. Altogether, these data seriously contradict to the deterministic sequential accumulation of mutations in the handful of «driver» cancer genes occurring in a continuous linear pattern of cancer progression.

Due to inability to find type- and stage-specific recurrent aberrations in solid tumors the multiple diverse numerical and structural chromosome changes in each tumor sample were disregarded and judged as a by-product of transformation by the conventional cancer gene mutation theory [23–28]. However, random aneuploidy/chromosome instability (CIN) and the resulting genomic heterogeneity significantly correlate with tumorigenic potential of cells [44–49], tumor disease progression from precancerous lesions to malignant tumors and then to metastases, patient survival [50–67], intrinsic and acquired (multi)drug resistance [68–84], and radioresistance [85–87]. Interestingly, there is a paradoxical relationship between extreme CIN and improved survival outcome in cancer [62, 88]. Tumors with extreme CIN display the highest chromosomal structural complexity and chromosomal numerical instability and are associated with improved prognosis relative to tumors with intermediate CIN [88]. It has been shown that missegregation of one or a few chromosomes per division (low CIN) promotes tumorigenesis, whereas missegregation of a larger number of chromosomes per division (high CIN) drives cell death and tumor suppression [89]. When CIN exceeds a certain threshold (in case of extreme CIN), it has a negative impact on cellular fitness [62]. Destabilizing aneuploidy generates nonneoplastic and nonviable cells [90]. Thus, CIN can both promote and constrain tumorigenesis [91–93].

According to the conventional cancer gene mutation theory tumors are addicted to a single activated oncogenic protein or pathway to maintain their malignant properties. Despite a recognized significantly high level of genomic and (epi)genetic heterogeneity within individual tumors, as well as between primary tumors, metastatic cells, and relapses [37–41, 52, 82, 83, 94–109], it is believed that acute inactivation of such oncogenic protein or pathway will result in a tumor regression (oncogene addiction concept) [110–117]. However, multiple diverse clinic trials have failed to demonstrate it [5–22].

Duesberg et al. have formulated questions, which the conventional cancer gene mutation theory has not explained: why a single transgene induces diverse cancers with different karyotypes, phenotypes, and complex transcriptomes; why the same transgenes produce conditionally reversible hyperplasias and dysplasias early and irreversible cancers late in conditional transgenic mice models [76, 80]; why cancer is caused by non-

mutagenic carcinogens; why cancer develops years to decades after initiation by carcinogens (long latent periods) and follows pre-neoplastic aneuploidy; why cancer is chromosomally and phenotypically unstable, generates much more complex phenotypes than conventional mutation, generates nonselective phenotypes such as metastasis and immortality [23–25]. The conventional genetic theory does not also explain the karyotypic changes that coincide with resistance, the high rates at which cancer cells acquire and enhance resistance compared to the rates of conventional mutation, the wide ranges of resistance such as multidrug resistance, and the frequent occurrence of intrinsic drug resistance [73]. These discrepancies have been explained by the evolutionary karyotypic theory of cancer [26–28, 73, 76, 80, 90, 118–122].

Now it is well documented that prior to the key stages of tumor progression (immortalization, transformation, metastases, and acquisition of drug resistance) a complex dynamic interplay between various stochastic non-clonal and clonal chromosome alterations is observed, and genomic instability and the resulting degree of both clonal and non-clonal heterogeneity are the interconnected driving forces of tumor evolution [73, 80, 76, 119–131]. The magnitude of intratumor heterogeneity correlates with clinical variables such as tumor progression, survival, treatment sensitivity, and the risk of acquired resistance. Moreover, genomic heterogeneity drives phenotypic heterogeneity observed among tumor cells and the evolution of karyotype is accompanied by changes in phenotype [76, 80, 101, 118, 120, 132–135]. Genomic instability is associated with profound changes in the transcriptome and proteome. Genome-wide analysis of DNA copy number alterations and mRNA expression shows a significant correlation in tumor samples [133, 136–142]. There is also moderate but still significant correlation between the change in global genes copy number and the corresponding proteins level [143, 144].

The evolutionary karyotypic theory of cancer has been developed and conceptualized mainly by P. Duesberg's [23–25, 76, 80, 118–120] and H. Heng's groups [26–28, 121, 122, 145, 146]. Studing karyotypic evolution in both individual cells and cell populations during various stages of cellular immortalization process using an *in vitro* cell culture model Heng's group has revealed that karyotypic evolution (macro-evolution) serves as the driving force for immortalization. There are two phases of karyotypic evolution. One is the discontinuous phase characterized by heterogeneous karyotypes within the same and between different passages of culture; the other phase is the stepwise continuous phase within which the majority of cells share similar karyotypes for hundreds of passages. These two phases represent punctuated (or macro-evolution) and Darwinian (or micro) evolution, respectively. Relationship between these two phases and genome system stability, measured by the level of stochastic genome alterations, has shown that the punctuated phase is characterized by genome system instablility (high frequencies of non-clonal chromosome aberrations (NCCAs), whereas the Darwinian stepwise phase demonstrates relative genome system stability (dominant clonal chromosome aberrations (CCAs) and low frequencies of NCCAs). Extremely high genome-level heterogeneity in the punctuated phase provides the genetic underpinning of the high degree of heterogeneity universally detected in cancers. By repeating the same experiments, or analyzing the parallel clones derived from the same initial cell population, it has been documented that the immortalized cells display unique distinctive karyotypes, demonstrating the stochastic nature of karyotypic evolution during cellular immortalization. Follow-up experiments have evidenced that karyotypic evolution can be detected in most of the major transition steps of cancer (immortalization, transformation, metastasis, and drug resistance), and all factors, genetic/non-genetic, internal/external, functioning as a stress to a given system, can contribute to cancer evolution (either through micro- or macro-evolution). Further, it has been demonstrated that karyotypic heterogeneity is linked to tumorigenicity. Using six well-characterized *in vitro* tumor progression models representing various types of cancer including human breast and prostate cancers as well as mouse ovarian cancer it has been shown that all sublines displaying high tumorigenicity, regardless of which molecular mechanisms were detected, are characterized by high levels of genome heterogeneity (the high frequencies of NCCAs). In contrast, all sublines with low tumorigenicity displayed distinctly lower frequencies of NCCAs. Heng et al. describe the evolutionary mechanism of cancer as three components/steps: stresses, the diverse cau-

ses of cancer, induce genome system instability; this instability produces genetic and epigenetic heterogeneity, which is essential for evolution; somatic cell evolution is based on a series of genome system replacements, which breaks the multiple system constraints (such as the tu mor suppressor function of genome integrity, tissue architecture, and immune system safeguards).

Meanwhile, by analyzing the karyotypes of clonal tumorigenic cell lines, derived from human cells transfected with the same set of artificially activated oncogenes, Duesberg's group has found that different tumorigenic cell lines have individual clonal phenotypes and basically stable karyotypes, although individually variable over many generations *in vitro*; that the phenotypes and karyotypes of different tumors induced by these lines in different mice, as well as drug-resistant sublines, derived from these lines, are karyotypic and phenotypic variants of the parental prototypes [76]. Stochastic, simultaneous multichromosomal rearrangements of cancer karyotypes generate metastases [120]. Duesberg's group proposed a two-step-mechanism of normal cell transformation to cancer cell [76].

First, carcinogens (mutagenic and nonmutagenic) as well as activated oncogenes trigger random aneuploidy. Aneuploidy destabilizes the karyotype by unbalancing teams of proteins involved in segregation, synthesis, and repair of chromosomes in proportion to the degree of aneuploidy.

Second, aneuploidy initiates and maintains karyotypic evolutions automatically due to the inherent instability of aneuploidy. Most of the newly evolving karyotypes are functionally inferior to those of normal cells or lethal. Occasionally, however, rare cancer-causing karyotypes evolve stochastically. These cancer-causing karyotypes are then stabilized against the inherent instability of aneuploidy by selection for transforming function within narrow clonal limits of variation. The resulting stability within instability of cancer karyotypes explains the flexibility and heterogeneity of cancer genome, which is the basis for the further spontaneous tumor evolution, such as metastasis and drug resistance [76].

Altogether, these findings support the concept that cancer initiation-progression and acquisition of drug resistance represent typical evolutionary processes and karyotypic evolution is the key event in cancer [26, 118–123, 146–153].

Cancer drug resistance: evolution of karyotype. Multiple mechanisms were proposed to contribute to general drug resistance: changes in transporter proteins, modulation of drug metabolism, enhanced repair of DNA damage, epigenetic mechanisms, tumor microenvironment, the selection of inherently drug refractory cancer stem cell populations or cancer-initiating cells [154–156]. The primary mechanism of acquired resistance during drug or antibody targeted therapy (e. g., inhibition of mutated EGFR, KIT, BRAF, ABL fusion, ALK fusion) proposed by the conventional cancer gene mutation theory of cancer is alterations within the gene that encodes the drug target (e. g., diverse second-site mutations, alternative splicing, gene amplification, and loss of gene rearrangement). Nevertheless, instead of exibiting alterations within the gene that encode the targeted protein the great proportion of tumor samples shows reactivation of the primary signaling pathways through constantly growing list of alternative signaling molecules [154, 157–167]. Moreover, multiple mechanisms of resistance may exist within a single tumor sample at the time of disease progression. According to the evolutionary karyotypic cancer theory karyotypic evolution/CIN is a dominant mechanism in endurement of cells with (multi)drug resistance [73]. Karyotypic evolution/CIN creates genomic, (epi)genetic, and phenotypic heterogeneity, causes global transcriptome and proteome changes, and rewiring of metabolic and signaling networks, altogether, giving rise to diverse drug-resistant variants. CIN is responsible for pre-treatment existance or acquisition during treatment of multiple mechanisms contributing to (multi)drug resistance. It is well documented that CIN significantly correlates with inherent and acquired (multi)drug resistance [68–84] and (multi)drug/chemoresistance acquisition is accompanied by new evolved chromosome imbalances [74, 76, 80, 81, 168–180]. In support, RNA and protein expression profiles after drug-resistance acquisition differ from parental drug-sensitive cells in expression of tens to thousands genes [174, 179, 181–189]. Acquisition of (multi)drug resistance in budding yeast *Saccharomyces cerevisiae* [190], human fungal pathogen *Candida albicans* [191], protozoan parasite *Leishmania* [192, 193], and *Cryptococcus neoformans* [194, 195] is also induced by aneuploidy. To the point, aneuploidy in yeast has been shown to provide significant growth ad-

vantages under severe genetic or environmental perturbations [196]. Even in *Escherichia coli* multidrug resistance is accompanied by significant changes in metabolism [197]; multiple mutations and substantial changes in gene expression are required to develop high level of resistance for most antibiotics in bacteria [198, 199].

Cytotoxic and targeted drugs used in clinic for standard cancer treatment, for example, such as nocodazole (microtubule-depolymerizing agents), paclitaxel and taxol (microtubule-stabilizing agents), platinum compounds cisplatin and carboplatin (alkylating agents), etoposide and doxorubicin (topoisomerase I and II inhibitors), bleomycin (causes breaks in DNA), actinomycin D (interferes with transcription and replication), 5-fluorouracil (thymidylate synthase inhibitor), imatinib and nilotinib (BCR-ABL inhibitors), rapamycin (mTOR inhibitor), and tamoxifen (estrogen receptor inhibitor) induce CIN/aneuploidy in rodent and human cells [74, 118, 168, 169, 200–206]. Drug-mediated stress can foster tumor evolution by both selecting genetic variations and generating novel variations through induction of genome reorganization [122]. Increase in chromosomal aberrations during and after chemotherapy was documented to associate with increased tumor aggressiveness [169, 185, 207, 208] and a higher risk of secondary tumor development [209–214]. Moreover, diverse cytotoxic drugs (e. g., bleomycin, cyclophosphamide, mitomycin C, and procarbazine) cause induction of germ line mutations [200, 209, 215] and transgenerational genome instability in mice [215, 216]. Targeted therapy (e. g., tyrosine kinase inhibitors) may also affect centrosomes and chromosome stability in disease-unrelated cells or tissues [54, 202–204]. Both cytotoxic and targeted therapies result in the multiple adverse long-term and delayed neurocognitive [217–219] and physical side effects [212, 220–231]. Similarly, antibody therapy has adverse side effects [228, 232–234]. To the point, cancer unrelated drugs are also far beyond safe. One must be concerned by a striking fact that 279 (52.1 %) out of 530 marketed pharmaceuticals ever tested for carcinogenicity have a positive response in at least one carcinogenicity assay in animals [235].

Thus, based on results of thousands of clinical trials there is no any known chemotherapy (including already clinically tested second generation therapy or synthetic lethal therapy) to which resistance of advanced-stage tumors would not develop and which would be lack of adverse side effects (fully not investigated and traceable yet but often long-term and delayed) [212, 217–235]. Furthermore, the future of truly effective cancer treatment is endangered by the output of cancer sequencing projects, which revealed hundreds of potential «druggable» targets [30–33]. Statistics says that there are more than 700 new drugs in the clinic, 300 to 500 drugs in development, and more than 10 000 clinical trials with 1200 drugs entering phase III studies [236]. All this medicine is still based on the conventional cancer gene mutation theory of cancer.

Perspectives. Human tumors display significant inter- and intratumor heterogeneity in various features including gene expression, gene mutations, epigenetic status, genome alterations, as well as histology, metastatic and proliferative potential. Both cancer sequencing and karyotype evolution/CIN studies strongly support the view that cancer evolution is not the sequential order of genetic alterations (specific cancer genes and common chromosome alterations) but, instead, can be described as «multiple cycles of punctuated and stepwise evolution where stochastic genome-level alterations [not gene mutations] are the key» [28, 122]. Todorovic-Rakovic states, «High-throughput oncogene mutation profiling now reveal all the complexity of cancer and provide the final explanation of the oncogenic pathways, based on stochastic (onco)genomic variation rather than on (onco)genic concepts» [237]. Consequently, the individual genes or pathways in tumors are clinically insignificant due to the unpredictable nature of pathway replacement as a result of genome evolution during cancer progression and upon treatment [28, 122]. Chemotherapy fails to prolong patient's lives in many cancers with heterogeneous and unstable genomes despite effective initial tumor response [122].

More and more researchers invoke the scentific community to pay attention to tumor evolution, intratumor heterogeneity and changes of intratumor heterogeneity during medical intervention [28, 95, 122, 237–241]. Karyotypic evolution and genomic heterogeneity generate the phenotypic plasticity driving neoplastic progression [28, 119, 122, 239]. There is urgent need to shift from the generally accepted view of cancer as a disease of genes into that of a genome-based disease,

and from analyzing tumors just as a bulk tissue to as a population of individual tumor cells [28, 122, 237, 238]. These important issues begin to be addressed [37– 41, 43, 242].

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О. А. Степаненко, В. М. Кавсан

Еволюційна каріотипова теорія раку *versus* загальновизнаної генної теорії раку

Резюме

Згідно із загальновизнаною генною теорією раку, протягом останніх десятиліть рак вважали генним захворюванням, яке виникає в результаті детерміністичного послідовного накопичення мутацій у невеликій групі ракових генів, що відбувається за лінійної прогресії пухлини. Однак на противагу цьому постулату у недавніх роботах із секвенування геному та екзому первинних пухлин і їхніх метастазів, а також окремих ділянок однієї і тієї ж пухлини виявлено величезну кількість стохастичних генних мутацій у кожній пухлині однакового типу та значну внутрішньопухлинну генетичну гетерогенність з «розгалуженою еволюцією росту пухлини» або «переривчастою клональною еволюцією без проміжних розгалужень», або «відсутність домінантних клонів у пухлинної тканині». Стохастичні каріотипові зміни і внутрішньопухлинну гетерогенність визнано провідною силою в еволюції пухлини і детермінантою розвитку терапевтичної резистентності і рецидиву. Еволюція каріотипу/хромосомної нестабільності і результуючий рівень внутрішньопухлинної гетерогенності суттєво корелюють з пухлиноутворювальним потенціалом клітин, прогресією пухлини від доброякісної до явно злоякісної та метастазування, а також з виживанням пацієнтів, чутливістю до хіміотерапії і ризиком виникнення резистентності. Обговорюється важливість еволюційної каріотипової теорії раку у розумінні біології раку і механізмів набуття стійкості до хіміотерапії.

Ключові слова: еволюція пухлини, каріотип, хромосомна нестабільність, внутрішньопухлинна гетерогенність, раковий ген, хіміорезистентність

А. А. Степаненко, В. М. Кавсан

Эволюционная кариотипическая теория рака *versus* общепризнанной генной теории рака

Резюме

Согласно общепризнанной генной теории рака, в течение последних десятилетий рак считали генным заболеванием, возникающим в результате детерминистического последовательного накопления мутаций в небольшой группе раковых генов, происходящего при линейной прогрессии опухоли. Однако в противоположность этому постулату в недавних работах по секвенированию генома и экзома первичных опухолей и их метастазов, а также отдельных участков одной и той же опухоли выявлено огромное количество стохастических генных мутаций в каждой опухоли одного типа и значительную внутриопухолевую генетическую гетерогенность с «разветвленной эволюцией роста опухоли» или «прерывистой клональной эволюцией без прослеживаемых промежуточных разветвлений», или «отсутствие доминантных клонов в опухолевой ткани». Стохастические кариотипические изменения и внутриопухолевая гетерогенность признаны ведущей силой в эволюции опухоли и детерминантой развития терапевтической резистентности и рецидива рака. Эволюция кариотипа/хромосомной нестабильности и результирующий уровень внутриопухолевой гетерогенности существенно коррелируют с опухолеобразующим потенциалом клеток, прогрессией заболевания от преопухолевого доброкачественного к явно злокачественному и метастазированию, а также с выживаемостью пациентов, чувствительностью к химиотерапии и риском приобретения резистентности. Обсуждается важность эволюционной кариотипической теории в понимании биологии рака и механизмов приобретения стойкости к химиотерапии.

Ключевые слова: эволюция опухоли, кариотип, хромосомная нестабильность, внутриопухолевая гетерогенность, раковый ген, химиорезистентность.

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