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Cancer stem cells: a paradigm shift in understanding cancerogenesis

The discovery of a minor cell population in tumors with features of tissue stem cells, which are called cancer stem cells (CSCs), has led to a new paradigm of cancerogenesis. According to this notion, many cancers (if not all) arise from CSCs, which renew themselves by asymmetric division (hierarchical model of cancerogenesis). A hierarchical model is distinct from a stochastic model, as the former is based on tumors arising not just from any tumor cell, but rather only from CSCs. The CSC concept bears answers to the most fundamental question of oncology, namely, how cancer cells relapse and metastasize after aggressive treatments including surgery and chemo- and radiotherapy. Therefore, understanding the biology of CSCs will open new avenues for cancer risk assessment, early detection, and prognostication as well as for developing new strategies for cancer prevention and therapies.
***Keywords**:* cancer stem cell (CSC), epithelial-mesenchymal transition (EMT), tumor microenironment, therapy resistance, natural killer (NK) cells.

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Қатерлі ісік бағаналы жасушалары: кансерогензды түсінүдегі жаңа парадигма

Қатерлі ісік бағаналы жасушалары (ҚІБЖ) деп аталатын ұлпалық бағаналы жасушалардың қасиеттеріне ие аз санды ісік жасушаларының табылуы кансерогенздің жаңа парадигмасына алып келді. Бұл тұжырым бойынша, басым көпшілік қатерлі ісіктер ҚІБЖ ның асимметриялы бөлінуі нәтижесінде пайда болады (кансерогенздің сатылы моделі). Сатылы модел кездейсоқ моделден өзгеше, өйткені алдыңғы модел ісіктің ҚІБЖ тан тарауын негіз етеді. ҚІБЖ консепциясы онкологияның ең фундаменталды сурақтарына жауап бере алады, яғни, қалайша қатерлі ісік жасушалардың өсуі агрессивті емдеулерден (хирургиялық, химия-радиотерапиядан) кейін де қайталанады және метастазданады. Сондықтан ҚІБЖ биологиясын түсіну ісіктің қатерлілігін бағалауға, ауруды ерте анықтауға, және прогностикаға сонымен қатар қатерлі ісіктің алдын алу стратегияларын дамытуға және емдеуге жаңа жол ашады.
Түйін сөздер: қатерлі ісік бағаналы жасуша (ҚІБЖ), епителиалдан месенкималға өзгеру (ЕМӨ), ісіктің шағын ортасы, емге төзімділік, натуралды киллер жасушалар

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Раковые стволовые клетки: смена парадигмы в понимании канцерогенеза

Открытие минорной клеточной популяции в опухоли со свойствами тканевых стволовых клеток, названной раковыми стволовыми клетками (РСК), привело к новой парадигме канцерогенеза. Согласно этому представлению, многие виды рака (если не все) возникают из РСК, которые самообновляются путем асимметричного деления (иерархическая модель канцерогенеза). Иерархическая модель отличается от стохастической, поскольку первая основана на возникновении опухоли не из любой опухолевой клетки, а только из РСК. Концепция РСК дает ответы на большинство фундаментальных вопросов онкологии, например, как опухоли рецидивируют и метастазируют после энергичного лечения, включая хирургию и химио- и радиотерапию. Поэтому понимание биологии РСК откроет новые перспективы оценки риска, ранней диагностики и прогноза опухолевой прогрессии, а также разработки новых стратегий предотвращения и терапии рака.
Ключевые слова: раковые стволовые клетки (РСК), эпителиально-мезенхимальный переход (ЭМП), опухолевое микроокружение, натуральные киллерные (НК) клетки.

During the past decade, a growing body of evidence has showed that tumors are not homogeneous mass of proliferating cells with equal genetic mutations as previously thought, but are organized in a hierarchy of heterogeneous cell populations with different phenotypic and functional properties [1]. As numerous reports demonstrated a distinct subpopulation of cancer cells, called CSCs (or tumor initiating cells), within tumor mass are responsible for maintaining the sustained tumor growth and relapse (or metastasis) after therapy. Therefore, in order to understand the clonogenic core of the cancer comprehensively, a number of groups have made great efforts in identification, isolation and characterization of CSCs from various hematologic and solid tumors on the basis of the shared phenotypic and functional properties with normal tissue SCs, namely, expression of surface antigens of corresponding normal SCs, ability of self-renewal and differentiation, resistance to conventional therapeutic strategies such as chemo- and radiotherapies, migration capacity and quiescence for a prolonged period of time [2]. Experimental evidences supporting the existence of CSC in various cancers have led to a paradigm shift in our understanding of cancer biology [3]. Moreover, the CSC model seemed to hold answers to some poorly understood clinical phenomena such as resistance to anticancer therapies, recurrence after such aggressive treatments and metastatic dissemination to distant organ sites resulting in most cancer patients' mortality [4].

Isolation and identification of CSCs

In 1997, Dick and colleagues have isolated CSCs from AML patient on the basis of combinatorial surface markers, $CD34^{+}CD38^{-}$, which also distinguish hematopoietic stem cells (HSCs) from their derivatives, and have proved the tumor recapitulating potential by transplanting into severe combined immunodeficient (SCID) mice [5]. Several years later, Clarke and colleagues applied the concept and experimental approaches to a solid breast tumor identified and isolated breast CSCs. In their xenograft assay, as few as 100 $CD44^{+}CD24^{-}$ cells can give rise to tumors that recapitulated the morphologic and immunophenotypic features of the original tumor, whereas tens of thousands of $CD44^{-}CD24^{+}$ cells could not form a tumor [6]. Subsequently, other researchers followed the similar approaches isolated and characterized CSCs from various types of human leukemias such as B-cell lymphoblastic leukemia, T-cell lymphoblastic leukemia [7] and solid tumors including prostate cancer, colon cancer, head and neck cancer, melanoma, lung cancer, liver cancer, brain cancer, ovarian cancer and mesenchymal carcinomas [8].

Currently, there are three main approaches widely used to identify, isolate and also gauge CSC potential from various cancer cell lines and patient-derived samples. Namely, cell sorting on the basis of cell surface markers using fluorescence activated cell sorting (FACS) and magnetic-activated cell sorting (MACS) methods; side population (SP) assay, in which CSCs efflux Hoechst 33342 dye by means of ATP-binding cassette (ABC) transporters, while differentiated cells do not; sphere forming assay, in which cancer cells with self-renewal capacities could form spheres and survive for a prolonged period of time in non-adherent serum-free culture conditions. Xenotransplantation assay, in which the sorted cancer cells were transplanted into immunodeficient mice, make it possible to gauge the clonogenic ability of the cells [8].

Origins of CSCs

Due to heterogeneity of CSCs in terms of functional and molecular aspects in the same tumor type [9, 10], the exact origin of CSCs has been remained the matter of debate. However, currently three origins of cells have been accepted as sources of CSCs: 1) bone marrow-derived cells (BMDCs), 2) resident adult tissue stem and/or progenitor cells, 3) differentiated cancer cell-derived CSCs through pathologically relevant epithelial to mesenchymal transition (EMT) program [11, 12]. Although, for a long time, local tissue stem cells have been viewed as the best candidate for CSCs, however, Wang's group has showed BMDCs may possibly serve as sources of CSCs at least in mouse models of Helicobacter-induced gastric cancer [13]. Apparently, this finding is still in its immaturity and needs further examination and validation.

As CSCs from various tumor types share the same surface antigens with corresponding normal stem cells, and also some reports suggests that the tissue stem and progenitor cells are more susceptible to oncogenic transformation than more differentiated cells, it was therefore hypothesized that tumors most possibly originate from these local tissue stem/progenitor cells [14]. For instance, Collins et

al. isolated tumorigenic prostate CSCs on the basis of high surface expression of integrin $\alpha_2\beta_1$ and CD133, which were used to isolate normal prostate epithelial SCs by the same group previously [15]. Brain CSCs were exclusively isolated from the cell fraction expressing the neural SC surface markers CD133 and nestin [16].

Although CSCs exhibit the SC traits of self-renewal and differentiation, they may do not necessarily originate from the transformation of normal tissue SCs. As recent studies have shown that the acquisition of CSC properties interlinked with the EMT program [17, 18]. EMT is a key embryonic developmental program that is also activated during wound healing and tissue repair, but, unfortunately hijacked by cancer cells in order to acquire the mesenchymal phenotypes as well as the abilities of mobility, invasiveness, anti-apoptosis and dissemination during tumor progression [19]. The association between CSC and EMT has made the CSC investigations even more complicated, mainly because, according to the cancer associated EMT model, CSC can be formed *de novo* from non-CSCs via receiving contextual signals from tumor associated microenvironment. If this is the case, simply targeting and eliminating preexisting CSCs is not sufficient to completely eradicate malignant disease from patients [20].

Resistance of CSCs to therapy

As mentioned above the ability of resistance to therapeutic interventions is largely due to the shared or acquired properties of normal SCs. Normally SCs have high DNA repair capabilities and express anti-apoptotic molecules [21]. For instance, glioma CSCs preferentially activate DNA-damage checkpoint resulting in faster DNA damage repair ability and escape ionizing radiation induced apoptosis. Breast CSCs also showed resistance to radiotherapy owing to overexpression of free radical-scavenging machinery in these cells. When pharmacologically inhibited the ROS scavengers the clonogenic potential of breast CSCs decreased and increased their sensitivity to radiotherapy [21]. One of the important resistance mechanisms of CSCs is attributed to their quiescence, because most current anti-cancer drugs tend to be more toxic to rapidly proliferating cells and after therapy is ceased, the tumorigenic CSCs resume growth, which clinically manifests itself as a relapse [22].

Targeting CSCs

Current cancer therapies often fail to eliminate advanced tumors. One reason for this failure is that most current cancer drugs destroy fast proliferating cells within bulk of tumor. Second reason comes from the intrinsic properties of CSCs shared with normal SCs, that is, more resistance to chemotherapeutic agents and radiation compare to mature/differentiated cell types from the same tissue. The second reason seems more challenging, because the key signaling pathways such as Hedgehog, Notch, PTEN, BMI-1, WNT, and p53 are involved in embryogenesis, morphogenesis and normal SC function during homeostasis [22, 23]. Targeting these physiologically essential signaling molecules can cause severe systemic side effects to cancer patients. Therefore, it will be important to develop CSC-selective therapies. An example of noncytotoxic strategy to deplete CSC activity came from an AML study, in which combination therapy with proteosome inhibitor MG-132 and the anthracycline idarubicin can lead leukemia SCs to apoptosis but not normal HSCs [24].

Prospective solution of CSC challenge may be expected from immunological approach. Studies from A.Jewett et al. [25] have shown that natural killer (NK) cells are capable of lysing CSCs, but within different tumor types these cells experience a condition known as ‘‘split anergy’’, whereby the NK cells lose the ability to kill CSCs and being to produce cytokines. As a result, uncontrolled tumor growth arises and tumor stroma accumulates anergic NK cells. Repeated allogeneic NK cell transplantation at the site of the tumor for elimination of CSC is proposed.

We hypothesized [26] that anergic tumor infiltrating NK (TINK) cells transmit their property to naïve NK cells by “infecting” them with a state of ‘‘split anergy’’ in a similar manner as T conventional cells are transformed into T regulatory cells during the process of ‘‘infectious tolerance’’. Anergic TINK cells egress from the tumor stroma via the lymphatic system, where they reach regional lymph nodes and transmit their properties to naïve NK cells, which in turn become anergic toward CSCs and lose immunosurveillance functions. Thereby development of the ways for anergic NK cell restoration into cytolytic activity status is a very urgent task.

As mentioned above, the importance of the microenvironmental signals which induce and promote CSCs, drives us to view CSCs as dynamic and flexible population rather than fixed one and to explore not only CSC-specific molecular mechanisms, but also CSC-inducible autocrine, paracrine and systemic signals that mediate vicious communications among cancer cells and activated stromal components.

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Создание кабинета диабетической стопы с целью профилактики и диспансеризации пациентов с синдромом диабетической стопы

Целью данного исследования явилось изучение социально-гигиенических характеристик заболеваемости и инвалидности вследствие диабетической стопы и установление степени ограничения различных видов жизнедеятельности вследствие диабетической стопы. В ходе исследования были сформированы 2 группы: исследуемая (27 человек) и контрольная (30 человек), изучили динамику заболеваемости и социально – гигиенические характеристики диабетической стопы в г. Караганде за период 2008-2013 г.г.; установили причины формирования инвалидности по диабетической стопе, степени ограничения различных видов жизнедеятельности при синдроме диабетической стопы.
Ключевые слова: синдром диабетической стопы, профилактика, диспансеризация, кабинет диабетической стопы.

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Диабеттік табан сидромын алдын алу және диспансеризациялау мақсатында науқастарға диабеттік табан бөлмесін құру

Диабеттік табан синдромымен ауыратын науқастардың жастық құрамы 61-70 жастан жоғары екенін көрсетіп отыр, яғни 44,7%, ал 71 жастан жоғары науқастар 25,9% құрайды. Аурудың түрін талдау жүргізу барысында, диабеттік табан сидромымен ауыратын науқастардың көпшілігі әйел адамдар, әйелдердің жастық құрамы 61-70 жас. Диабеттік табан синдромымен аурыратын науқастарға жасаралық және әлеуметтік талдау жүргізгенде науқастардың жасы 61-70 басым болып отыр және олардың барлығы жұмыссыз, науқастардың ауру ұзақтығы 6-10 жыл. Диабеттік табан синдромы кезіндегі науқастарда II деңгей – 66,6% жағдайда кездеседі.
Түйін сөздер: Диабеттік табан синдромы, алдын алу, диспансеризациялау, диабеттік табан бөлмесі.

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The creation of the diabetic foot cabinet for preventive measures and health assessment of patient with diabetic foot syndrome

Analysis of diabetic foot patients suffering from diabetic foot showed that in age structure predominate patients aged 61-70 years or 44,7% and 71 and over amounts 25,9%. Thus, majority of people suffering from diabetic foot were women and analysis of the form of disease at women found that prevails age 61-70. Analysis of the demographic and social situation of patients with diabetic foot showed that prevalence of patients ranging in age from 61 to 70 years with predominance of the number of unemployed. Disease durations analysis of diabetes mellitus patients showed that most of the people have diabetes mellitus for 6-10 years. In diabetic foot structure predominate second stage – in 66,6% of case.
Keywords: diabetic foot syndrome, prevention, clinical examination, diabetic foot cabinet.

Развитие гангрены стопы у больных сахарным диабетом является основной причиной ампутации конечности более чем у 50% больных, послеоперационная летальность составляет 13-20%. В течение 3 лет после ампутации 35% больных погибают.

В системе оказания помощи этой категории больных особенно страдает амбулаторное звено. Отсутствие кабинетов диабетической стопы, с педиатрической подготовкой врачей и медицинских сестер. Диспансеризация пациентов и профилактика синдрома диабетической стопы оказывается недостаточно эффективной, а зачастую вообще не проводится.

Целью данного исследования явилось изучение социально-гигиенических характеристик

заболеваемости, инвалидности и установление степени ограничения различных видов жизнедеятельности вследствие синдрома диабетической стопы.

Задачи исследования:

Изучить динамику заболеваемости и социально-гигиенические характеристики диабетической стопы в г. Караганде за период 2008-2013г.г.

Установить причины формирования инвалидности по диабетической стопе, степени ограничения различных видов жизнедеятельности при наличии синдрома диабетической стопы.

Материалы и методы

Материалом для изучения социально-гигиенических характеристик синдрома диабетической стопы и инвалидности по причине диабетической стопы послужили сформированные 2 группы: исследуемая 27 человек и контрольная 30 человек, средний возраст пациентов 45-76 лет, в группы входят как мужчины, так и женщины.

Результаты и их обсуждение

Анализ формы заболевания выявил, что большинство лиц, страдающих диабетической стопой (ДС), составили женщины от всего числа наблюдаемых с СДС – 81,5% в количестве 22 человека. Анализ возрастного состава больных СДС показал, что преобладают больные в возрасте старше 61-70 лет человек или 44,7% и от 71 и старшее составили 25,9%.

Таким образом, большинство лиц страдающих СДС, составили женщины, причем анализ формы заболевания выявил, что у женщин, чаще в возрастной группе 61-70 лет. Анализ половозрастного и социального положения больных диабетической стопой показал, что превалирует больные в возрасте от 61 до 70 лет с преобладанием числа неработающих. Анализ длительности заболевания больных сахарным диабетом показал, что большая часть были со сроком диабета от 6 лет до 10 лет. В структуре ДС преобладала II стадия – в 66,6% случаев.

Выводы: Анализ заболеваемости пациентов с диагнозом «диабетическая стопа» в условиях стационара «Городской больницы №1» и «Областного медицинского центра» города Караганды показал, что купирование гнойно-воспалительного процесса удалось достичь в 71% случаев, ампутация пораженной конечности потребовалась в 29%, летальный исход 7% . Для улучшения профилактики и диспансеризации пациентов с синдромом диабетической стопы рекомендуется открыть кабинет диабетической стопы при ПМСП. Мировая практика показала, что работа кабинетов диабетической стопы улучшает показатели в диагностике синдрома остеоартропатии у лиц из группы риска, а также снижает уровень заболеваемости СДС при проведении профилактической работы.

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