НАУКОВІ СТАТТІ

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ON THE NOTION OF SYNERGY OF MONOCLONAL ANTIBODIES AS DRUGS

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History of developing synergy between monoclonal antibodies, anti-tumor activity of monoclonal antibodies against tyrosine-kinases receptors EGFR/ErbB-1 and HER2/ErbB-2 as well as growth factor VEGF in various combinations are considered in the article. There were proposed hypotheses about potential molecular mechanisms underlay synergy between monoclonal antibodies (for homo- and hetero combinations of antibodies appropriately specific for antigenic determinants on the same or different receptors). Future trends in researches necessary to deeper understanding causes of this phenomenon and perspectives for practical application of monoclonal antibodies acted synergistically as immunotherapeutic drugs for human tumors treatment are reviewed.

Key words: monoclonal antibodies, epidermal growth factor receptors EGFR/ErbB-1 and HER2/ErbB-2, vascular endothelial growth factor (VEGF), synergy, molecular mechanisms, tumor immunotherapy.

Efforts to initiate a specific approach to immunotherapy of cancer started with the attachment of chemotherapeutic drugs by a weak covalent link to antitumor antibodies, at that stage still polyclonal [1–3]. Spacers such as dextran or polyglutamic acid were used to allow high drug load. At a later stage the antibodies were biotinylated, whereas the drug was attached to avidin, allowing a two stage drug targeting to the tumor [4]. During these experiments we noted that there was no need to covalently attach the drug to the antibody, which by itself had some antitumor activity. For example, when monoclonal antibodies (mAbs) to epidermal growth factor receptor (EGFR) were injected together with cisplatin [5] they exerted a strong synergistic effect on the ability to reduce the size of tumors (KB human epidermal carcinoma). This early observation, of a synergistic effect on cancer between an antibody and a chemotherapeutic drug, has paved the way for an extensively used clinical protocol [6] .

To further explore ways to enhance therapeutic efficacy, we addressed the mechanism underlying tumor inhibition by mAbs to receptor tyrosine kinases such as EGFR/ErbB-1 and HER2/ErbB-2. One mechanism attributes tumor growth inhibition to the ability of anti-receptor mAbs to induce endocytosis and degradation of the receptors. The mAbs down-regulate the receptor leading to attenuated ligand-induced signaling potency and duration. To enhance antibody-mediated endocytosis of these cancer-causing receptors we introduced combinations of mAbs and found that epitope-distinct mAbs to the same receptor (homo-combination) can significantly enhance the rate of receptor breakdown in KB cells over-expressing EGFR [7]. Further, when combined, the mAbs synergize in terms of growth inhibition of N87 human gastric carcinoma over-expressing HER2 [8]. The combinations act in synergy if they are directed against distinct epitopes, i.e. sufficiently remote from each other on the receptor. The mAbs then cross-link the receptors and efficacy of immunotherapy is attributed to receptor cross-linking and size of antibody-receptor clusters formed at the cell surface. The clusters are rapidly removed, a step which dictates the rate of endocytic clearance, receptor down-regulation and extent of signaling blockade [6].

A mechanistically distinct approach simultaneously targets two different receptors, such as targeting both EGFR and HER2 (hetero-combination) or a receptor (e.g., HER2) and an anti-angiogenic growth factor (VEGF,

using Avastin-bevacizumab). The extracellular domain of human ErbB presents adjacent or over-lapping determinants harboring multiple antigenic sites. Depending on the site, a mAb can be dormant, propagate tumor growth or mediate a distinct detrimental effect. It can disturb ligand binding, interfere with heterodimer formation that induce signal transduction, or interfere with any other pathway not yet identified. Scientific rationale suggests that combining two mAbs to two epitopes on the same receptor, or two mAbs to the two receptors, can target different pathways. They may perturb the cancer cell by inducing a collaborative damage of simultaneously impaired functions often by differing but complementary mechanisms of action of the two mAbs.

While conducting experiments with various combinations of antibodies to HER2, we noted an interesting observation: an antibody which by itself exerted no effect on tumor growth in animals was nevertheless able to enhance the tumor-inhibitory effect of an otherwise weakly inhibitory mAb. Another interesting observation relates to the target epitopes. Our most effective mAb combinations always included an antibody directed to the dimerization arm of HER2, a region permitting HER2 to form heterodimers with EGFR and ErbB-3. Whether these observations can be generalized and applied to tumor markers other than HER2 is an intriguing issue, the elucidation of which requires additional investigation and broader repertoires of mAbs to HER2. The current challenge is to identify pathway-specific therapies and explore their potential additive or preferably synergistic effects, while avoiding excessive toxicities.

Our study was recently extended to human pancreatic carcinoma, a malignancy with extremely poor prognosis, which is largely considered incurable. We compared the effects of nine homo- and hetero-combinations of mAbs to EGFR or HER2, on the growth of human pancreatic carcinoma BXPC3 expressing moderate level of EGFR and low level of HER2. MAbs to the two receptors inhibited tumor growth in animals as single agents but acted in synergy and were more effective when paired in homo-combinations, exerting improved inhibition. Anti-HER2 mAbs, despite the low HER2 receptor, acted as important partners in collaborating with mAbs to EGFR to form highly inhibitory pairs. These hetero-combinations acted in synergy and were the most effective in generating long-term inhibitory activity.

The low effectiveness of therapeutic mAbs and the evolution of patient resistance call for deeper understanding of mechanisms that underlay immunotherapy. Because the superiority of mAb combinations extends to tumor cell cultures, it may be assumed that in addition to cellular responses, non-immunological mechanisms also contribute to antibody synergy. Translation of these lessons to clinical applications may enhance patient response and delay acquisition of resistance.

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КОНЦЕПЦІЯ ВИКОРИСТАННЯ СИНЕРГІЇ МОНОКЛОНАЛЬНИХ АНТИТІЛ ДЛЯ СТВОРЕННЯ ЛІКАРСЬКИХ ПРЕПАРАТІВ

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Розглянуто історію відкриття явища синергічності моноклональних антитіл, результати досліджень протипухлинної активності їх різних комбінацій проти рецепторів тирозинкіназного EGFR/ErbB-1 і HER2/ErbB-2, а також фактора росту VEGF. Висловлено припущення про можливі молекулярні механізми, що лежать в основі явища синергічності моноклональних антитіл (для випадків гомо- і гетерокомбінацій антитіл, специфічних відповідно до антигенних детермінант одного й того самого або двох різних рецепторів). Обговорено напрями подальших досліджень, необхідних для глибшого розуміння причин цього явища, а також перспективи практичного застосування імунотерапевтичних препаратів на основі синергічних моноклональних антитіл для лікування пухлин людини.

Ключові слова: імунотерапія пухлин, моноклональні антитіла, синергічність, рецептори епідермальних факторів росту EGFR/ErbB-1 і HER2/ErbB-2, ендотелію судин (VEGF).

КОНЦЕПЦИЯ ИСПОЛЬЗОВАНИЯ СИНЕРГИИ МОНОКЛОНАЛЬНЫХ АНТИТЕЛ ДЛЯ СОЗДАНИЯ ЛЕКАРСТВЕННЫХ ПРЕПАРАТОВ

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Рассмотрены история открытия явления синергичности моноклональных антител, результаты исследований противоопухолевой активности их различных комбинаций против рецепторов тирозинкиназных EGFR/ErbB-1 и HER2/ErbB-2, а также фактора роста VEGF. Высказаны предположения о возможных молекулярных механизмах, лежащих в основе явления синергичности моноклональных антител (для случаев гомо- и гетерокомбинаций антител, специфичных соответственно к антигенным детерминантам одного и того же либо двух различных рецепторов). Обсуждены направления дальнейших исследований, необходимых для более глубокого понимания причин этого явления, а также перспективы практического применения иммунотерапевтических препаратов на основе синергических моноклональных антител для лечения опухолей человека.

Ключевые слова: иммунотерапия опухолей, моноклональные антитела, синергичность, рецепторы эпидермальных факторов роста EGFR/ErbB-1 и HER2/ErbB-2, эндотелия сосудов (VEGF).