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Review

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Review

Special Review: The future of Immunotherapy

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Summary

During the last two decades, two main schools of modern immunotherapy have come to the forefront. The chimeric anti-CD20 antibody rituximab that was introduced for the treatment of refractory follicular lymphoma in 1998 was one of the first examples of the school of passive immunotherapy. Subsequently major and ever more costly efforts were spent on the development of blockbuster monotherapies including other monoclonal but also bispecific antibodies of highly defined specificity and subclass, antibody–drug conjugates (ADCs), as well as *ex vivo* expanded tumor-infiltrating lymphocytes, chimeric antigen receptor (CAR)-transduced T cells, and TCR-transduced T cells. On the other hand, there is the school that works toward active induction of patient B- or T-cell immunity against antigens of choice, or active tolerance against pathogenic allergens, auto-antigens or allo-antigens. Stradled in between these two approaches is treatment with blockers of T cell checkpoint control, which releases the brakes of T cells that have already responded to antigen. Extensive and detailed insight into the cellular and molecular interactions that regulate specific immune responses is indispensable in order to be able to optimize efficacy and rule out treatment related toxicity. This applies to all types of immunotherapy. Our knowledge of the checks and balances in the immune system is still increasing at an unprecedented pace, fostering ever more effective and specific (combination) immunotherapies and offering a rich harvest of innovative immunotherapies in the years ahead.

Keywords: immunotherapy, monoclonal antibody, T cell, vaccination, immuno-modulation

Introduction

Immunotherapy has now expanded into vast areas of medicine, including the treatment of infectious diseases, allergy, inflammatory disease, auto-immune conditions, and cancer. In auto-immune diseases, transplantation, and allergy, the holy grail of treatment is specific tolerance induction rather than immunosuppression or symptom suppression by monoclonal

Abbreviations: ADC: Antibody–drug conjugate; ATC: Adoptive T cell therapy; BiTE antibody: Bispecific T cell engager antibody; CAR: Chimeric antigen receptor; hrHPV: High-risk human papilloma virus; MoAb: Monoclonal antibody; NK cell: Natural killer cell; SLP: Synthetic long peptide; TCR: T cell receptor; TME: Tumor micro-environment.

antibodies. Prevention of disease is increasingly based on insight into the same immunological mechanisms that have served us more recently regarding the development of novel therapeutic strategies. Since times immemorial, preventive vaccines have relied on the induction of high levels of antibodies that neutralize, opsonize, or lyse invading microorganisms (bacteria and viruses) or inactivate their major toxin(s). However, textbooks of immunology teach us that for established virus infections antibodies are no good, and that infected cells are effectively dispensed with by cell-mediated immune mechanisms only. Indeed, T cells are not distracted by freely floating antigen in body fluids. They kill virus-infected cells with microsurgical precision and effectiveness as these are recognized by viral peptide presentation in human leukocyte antigen (HLA) molecules. In what follows I will argue that preconceived ideas about the immune effector mechanisms needed for prevention as well as disease-modifying purposes are no longer valid, thanks to novel biotechnology and new insights into prevention and therapy. Nevertheless, we still need the basic principles that dictate that antibodies have been designed to primarily cleanse the body fluids from extracellular organisms such as extracellular bacteria, whereas T cells primarily clear the body cells of intracellular organisms such as viruses.

Innovative applications of monoclonal antibodies and T cells

Infectious disease

Monoclonal antibodies

Human monoclonal antibodies (MoAbs) of choice can now be produced very efficiently, thanks to the capacity of hybridoma cells to produce MoAbs of pre-defined specificity, avidity, and immunoglobulin subclass in unlimited quantities, derived from B cells of infected or immunized patients or from mice with a completely humanized immunoglobulin gene and T cell receptor (TCR) repertoire. This has even opened the doors for the treatment of severe established virus disease with monoclonal antibodies, such as established Ebola virus infection [1] or (in mice) Middle East Respiratory Syndrome infection [2]—with some degree of success. In the case of established Ebola virus infections, the death rate after antibody treatment was reduced from over 50% to 33.5% [1]. Therefore, this concept is currently being explored (further) for the treatment of established infections with the scourge of the current era: SARS-CoV-2. Still, these treatments can only operate by neutralizing new extracellular progeny virus released from dying cells, thereby halting the spread of the virus to other cells. MoAb treatment cannot be expected to replace the unsurpassed efficacy of T cell-mediated killing of live virus-infected cells. The reasons are simple: antibodies have insufficient access to intracellular viral antigens, and T-cell-mediated killing appears to be more effective at eradicating surface antigen-positive cells than antibody-dependent cellular cytotoxicity or complement-dependent lysis of cells. Obviously, the lack of HLA restriction of anti-viral MoAbs makes them attractive and broadly applicable for the treatment of every infected patient. However, treatments with the capacity to rapidly generate virus-specific $CD4^+$ and $CD8^+$ T cells as well as activated NK cells through rapid response initiation or transfusion of TCR-transduced patient-derived T cells should be far more effective than MoAbs when it comes to getting rid of the infection. A parallel can be drawn here between the much greater efficacy of chimeric antigen receptor (CAR) T cells in eradicating B cell malignancies than that of MoAbs against the same CD19 and CD20 B cell antigens (see below).

Therapeutic vaccines

Surprisingly, therapeutic vaccines for virus-induced diseases have not yet been registered, with the exception of a rabies vaccine, but their design and manufacture is straightforward, comparable to the production of therapeutic cancer vaccines [3, 4], and directed at powerful effector and memory T cell induction. Surprisingly, we know that virus infections are most effectively cleared by NK cells and T cells, but to date all preventive anti-viral vaccines rely on the induction of neutralizing antibodies. A more effective way to deal with both prevention and control of established virus infections would be rapid mobilization of T cells alongside neutralizing antibodies. Indeed, many of the persons who spontaneously cleared SARS-CoV-2 infections showed no evidence of serum antibodies against the virus, but merely displayed memory T cell responses [5]. COVID-19 is a disease in which both rapid deployment of effective preventive vaccines is needed as well as testing and tracing of recently infected people. A therapeutic vaccine can help to prevent exacerbation of disease in early infected persons at risk of full blown disease by induction of a faster and more powerful effector and memory T cell response than this person would otherwise develop spontaneously. Therapeutic vaccines will likely be developed against not only SARS-CoV-2, but also other viruses that mediate subacute or chronic diseases. Such therapeutic vaccines will typically be built on plasmid DNA, RNA, or synthetic long peptide (SLP) vaccine platforms, rather than viral vectors. The biologic activity as monotherapy of two of these modalities (SLP and plasmid DNA vaccines) has already been proven in the case of pre-malignant lesions

caused by high-risk human papilloma virus (hrHPV) such as HPV16 [3, 4]. Similar therapies can be developed for other chronic persistent virus infections such as hepatitis B and associated conditions.

Cancer

Bispecific antibodies, ADCs, and CARs

Bispecific antibodies and ADCs have proven their value as effective anti-cancer therapies, and several of these agents have been approved since the early 2000s, especially in the context of therapy-resistant B cell leukemias, lymphomas, and acute myeloid leukemia [6–8]. The bispecific T cell engager (BiTE) antibody blinatumomab has dual CD3 and CD19 specificity. Its mode of action is to non-specifically engage $CD3^+$ T cells to kill $CD19^+$ malignant B cells, for example, B-ALL cells, by bringing them into close contact with each other [7]. In 2014, blinatumomab was approved to treat Philadelphia chromosome-negative relapsed or refractory B-cell precursor acute lymphoblastic leukemia (in first or second remission) in adults and children.

ADCs are complex molecules composed of an antibody linked to a biologically active cytotoxic (anticancer) payload or drug. ADCs combine the targeting capabilities of monoclonal antibodies with the cancer-killing ability of cytotoxic drugs; examples of registered agents are gemtuzumab ozagomycin (AML) [8] and trastuzumab emtansine (HER2-positive breast cancer) [9]. Gemtuzumab is a monoclonal antibody to CD33 linked to a cytotoxic agent from the class of calicheamicins; trastuzumab coupled with a linker to maytansine has been approved for the treatment of metastatic HER2-positive breast cancer since 2013.

T cells transduced with chimeric antigen receptors (CARs) have proven to be a powerful cellular anti-tumor approach, utilizing the exquisite specificity of antibodies coupled to the powerful effector function of T cells against (cancer) cells. The other successful approach to cause T cells to kill $CD19^+$ leukemia or lymphoma cells is transduction of the T cells with a chimeric antigen receptor (CAR) [10], consisting of the antigen binding domains of a monoclonal anti-CD19 antibody coupled to the constant domain of the α/β TCR. A special required feature for efficacy is the incorporation into the CAR of the signaling domain of either CD28 or 4-1 BB (CD137). Such a signaling domain makes the transduced T cells independent of the usual checks and balances regulating T cell responses, allowing their virtually unbridled antigen-driven expansion and persistence. Because of their powerful T cell activating properties, BiTEs, ADCs, and CAR-transduced T cells can cause a severe cytokine release syndrome in hematological malignancies [11]. This can either be prevented by cancer cell reducing measures in the case of BiTEs or by treatment with anti-IL-6 in the case of CAR-transduced T cell transfusion [11]. Another undesirable long-term side effect of anti-CD19 CAR T cell therapy is permanent depletion of normal B cells, necessitating supplementation therapy with immunoglobulins from pooled healthy donor plasma. It is likely that in the near future, it will become possible to have the CAR T cells destroy themselves through a built-in suicide gene that can be activated by a simple non-toxic drug. Obviously, this can only happen if very sensitive techniques have ascertained the complete absence of malignant B cells. Only in these circumstances, it is safe to eliminate the therapeutic CAR-transduced T cells from the body. So far, CAR T cells have shown excellent biological activity against hematological malignancies such as B cell leukemias and lymphomas. It has proven much harder to find good targets for CAR T cells on the surface of solid malignancies, but solid cancer-specific CAR T therapy has already been developed for prostate-specific membrane antigen and mesothelin [12, 13]. Therapy escape by loss of antigen expression can be avoided by the use of bispecific CARs, in the case of B cell malignancies directed against at least two B cell-specific antigens, for example, CD19 andCD20 [14].

Adoptive T cell therapy

Taking tumor-infiltrating T lymphocytes (TILs) or T cells from blood and expanding them for therapy of cancer has taken a big flight and has shown remarkable proof of concept, in particular in metastatic melanoma [15] and virus-induced malignancies [16]. In addition, αβ TCRs from T cell lines or clones, usually $CD8^+$ T cells directed against epitopes presented by frequent HLA class I molecules, can be transduced into random T cell populations of cancer patients, again often melanoma [17, 18]. Like CAR T cell therapy, TCR transduction therapy is a form of somatic gene therapy. It is therefore personalized, and currently laborious and expensive, but efforts to use allogeneic T cells for off-the-shelf therapy are ongoing. An optimal antigen-driven effector $CD8^+$ T cell response in addition to an optimal memory $CD8^+$ T cell response requires simultaneous antigen recognition of HLA class II-presented epitopes on dendritic cells (DC) by $CD4^+$ T cells. Usually, the intricate cognate cell interactions between $CD4^+$ T cells, $CD8^+$ T cells, and DC are not mimicked in TCR transduction therapies because this would require simultaneous transduction of $CD4^+$ T cells with an HLA class II epitope-recognizing TCR. This would make this type of therapy even more complex and hard to implement. Progress in this area is likely to come from similar improvements as have made the difference in CAR T cell

therapies. CARs could be made much more efficient by insertion of a CD28 or a 4-1BB signaling domain. There is no reason why transduction of classical αβ TCRs could not be made equally efficient and independent of $CD4^+$ help and/or T cell checkpoint control by the insertion in the TCR of similar signaling domains, provided that potential toxicity can be suppressed by a built-in TCR turn-off mechanism, activatable by a simple drug. In addition, escape from immunotherapy by loss of expression of a single HLA class I molecule should be minimized by transducing patient T cells with TCRs specific for CD8 epitopes presented by at least two distinct HLA class I molecules. The obvious advantage of TCR transduction therapy is that target structures can include peptides from the entire intracellular proteome as opposed to just the cell surface in the case of CARs that depend on immunoglobulin variable domains for specificity.

Therapeutic vaccines, checkpoint blocking, and combination immunotherapy

More often than not immunosuppressive conditions prevail in cancer tissues and their stroma, as summarized under the term T cell-hostile tumor micro-environment (TME). This is exemplified by the fact that pre-malignant lesions caused by hrHPV16 can be effectively treated with therapeutic vaccines as monotherapy [19–22], whereas late-stage recurrent or metastatic cancers at the other end of the disease spectrum require combination therapies of vaccination in combination with anti-PD-1 checkpoint blocking [23] or chemotherapy [24]. Curiously, checkpoint blockers, such as anti-PD-1 or anti-CTLA-4, when injected intravenously at high dose cause substantial inflammatory or auto-immune side effects. However, local delivery of a CD40 agonist or CTLA-4 checkpoint blocker MoAb into the draining lymph node area of a tumor lesion at lower dose, and in a slow release, vehicle is just as effective in mouse models. Furthermore, this approach is not associated with the aforementioned side effects, although it generates a systemic T cell response of equal magnitude [25, 26]. Combination of monoclonal antibodies against the two T cell checkpoints CTLA-4 and PD-1 has successfully increased the clinical response rate in metastatic melanoma, but at a price of increased toxicity [27]. This combination may in particular benefit from slow release local delivery. Other therapeutics that can be combined with ACT or therapeutic vaccination are improved versions of γC cytokines, FLT3 Ligand, anti-TGFβ, and many other immunomodulators in the pipeline [28]. The challenge in late-stage disease is to define what the precise immunological TME deficiencies are in each individual patient, in order to be able to select the tailor made most effective combination therapy for that patient, requiring sophisticated precision biomarker analyses [28]. In addition, the selection of the best target(s) for therapeutic T cells in each patient with a non-viral mutation-based cancer must be individualized by defining the immunogenic mutation-based neoepitopes in that patient [29, 30]. Ideally, the mutations are contained in mutant driver molecules of the malignancy, ensuring ubiquitous expression in all malignant (sub)clones and avoiding easy immune escape by antigen loss during clonal evolution of the malignant cells [28].

Specific immunological tolerance induction in allergy, auto-immune disease, and transplantation

Allergy

In allergic disease such as atopic eczema and bronchial asthma, monoclonal antibody therapy such as anti-IL-4 receptor MoAb can alleviate symptoms [31], but an even more specific and permanent solution is to channel the specific immune response away from pathogenic Th2/IgE responses. This can in theory be achieved whenever the target T and B cell epitopes of disease-causing immune responses are known. While current desensitization therapies are based on this principle [32], such immune deviation can most likely be achieved in a much more precise, predictable, and rapid fashion by peptide vaccines against these allergens with extreme Th1-polarizing platforms [33, 34].

Auto-immune disease

Both organ-specific and systemic auto-immune diseases are traditionally treated with either non-specific immunosuppressive drugs or antibodies depleting cytokines, B cells, or activated T cells, depending on whether the disease is thought to be primarily caused by antibodies or by T cells. Complete pathogenic B cell depletion may require CAR T cell therapy against CD19/20 as discussed above for B cell-derived lymphoma/leukemia, followed by auto-elimination of the CAR T cells, allowing regeneration of a normal B cell repertoire without pathogenic B cell clones. A more attractive option is specific tolerance induction against the pathogenic antigen(s) (reviewed in ref. [35]), including induction of antigen-specific $FoxP3^+$ regulatory T cells). Unfortunately, the precise T- and/or B cell antigens causing auto-immune disease are often still unknown for many diseases. A complicating factor is that multiple target antigens may be presented by multiple HLA class I and II molecules to pathogenic $CD4^+$ and $CD8^+$ T cells.

Transplantation

Effective survival of allografts, like treatment of autoimmune diseases, still largely depends on non-specific immunosuppression—whether that be chemical or biological suppression—on top of tissue matching. However, although donor-specific tolerance induction is a theoretical possibility, it has not reliably succeeded with the possible exception of liver allografts, which benefit from the tolerogenic properties of the immune environment in the liver [36]. Much work thus remains to be done. It proved possible to successfully treat organ/tissue recipients with several types of tolerogenic DC of donor origin in mouse, rat or non-human primate allo-transplantation and clinical trials are ongoing [37].

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C.J.M.M was the sole author of this manuscript.

Conflict of interest

I am employed as chief scientific officer of biotech company ISA Pharmaceuticals, developing therapeutic vaccines against cancer.

Data availability

All data in this article are available from the cited literature or, when I dealt with future immunotherapeutic modalities, still need to be proven by future experiments and clinical trials.

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