pH-Responsive Vaccine Delivery System in Cancer Vaccines Formulation

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Cancer vaccination as an immunotherapy to increase the immune system's anti-tumor immunity has been extensively studied. Extracellular and intracellular pH measurements reveal that the endocytic spaces of DCs have a somewhat acidic pH. While being surrounded by endosomal structures, proteases are more quickly destroyed as a consequence of antigen import by endocytosis and the consequent acidification of the lysosome. Low endosomal pH is a suitable internal signal for pH-responsive vaccine delivery techniques for regulating antigen production. Reacting to changes in pH, this intracellular distribution may be achieved by using acid-catalyzed disintegration, particle phase shift, and the "proton sponge effect". When it comes to the administration of cancer vaccines, pH-responsive biomaterials have attracted the greatest attention.

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1. Acid-Labile Biomaterials with the Ability to Change pH

Making pH-responsive cancer vaccines is simple, as acid-labile polymeric NPs are used to encapsulate vaccine components. Certain molecular linkers are stable at neutral or slightly basic pH, but a rapid breakdown in acidic cellular compartments forms the foundation of this kind of vaccine carrier.

A rapid increase in the number of antigen molecules disturbs the endosomal membrane, enabling antigens released from ruptured endosomes to be released more easily. Polymeric NPs for immunization delivery were pioneered by the Fréchet group and others [1][2]. Making use of microgel linkers that cross-linked polymer chains to create an acid-labile ketal-derived moiety, they created a vaccine delivery system that adjusts to the surrounding pH level.

Polyacrylamide and degrading polyurethanes may be used to create a variety of cross-linked biomaterials [3][4]. pH-responsive vaccination significantly boosted the CD8+ T cell cross-priming and effector function in mice versus vaccines that were not sensitive to pH changes or that were less responsive. A DC-targeting antibody may be added to particle vaccinations to boost their ability to target DCs [5][6].

The first-time antigenic proteins were delivered to DCs, they were not accompanied by adjuvants. When DCs were exposed to an acid-labile delivery method, there was an increase in DCs' ability to secrete adjuvant chemicals intercellularly [7]. An imidazoquinoline derivative, acting as a small-molecule TLR7/8 agonist, was covalently

bonded to each chain of the polymeric nanogel [7]. At the endosomal pH of nanogel vaccines, adjuvant administration tests have demonstrated a significant increase in effectiveness and safety.

For greater therapeutic effectiveness, it was shown that combining nanogels' temperature and pH responsiveness boosted the targeting and retention of adjuvants [8]. A dual-responsive system may control the tissue and intracellular delivery of a cancer vaccine.

For a cancer vaccine to be successful, the antigen and adjuvant must be injected concurrently. Several prior investigations [9] have shown this to be true.

Using responsive biomaterials, co-delivery has been accomplished. The acid-degradable MOF-based NP was developed by Duan et al. for the delivery of melanoma antigens and adjuvants by coordinating lanthanide ions with GMP (**Figure 1**) for both encapsulation and surface binding. This MOF-based delivery mechanism was loaded with an ovalbumin (OVA) model antigen, and Watson–Crick base pairing permitted the integration of an adjuvant, a TLR-9 antagonist, in a simple one-pot approach. MOF-sized nanoparticles' LN and DC internalization strategies were fine-tuned for this aim (with a 30 nm diameter). The B16-OVA mouse model, which expresses the OVA gene, was vaccinated more successfully and efficiently using a formulation that degraded quickly at pH 5.0.

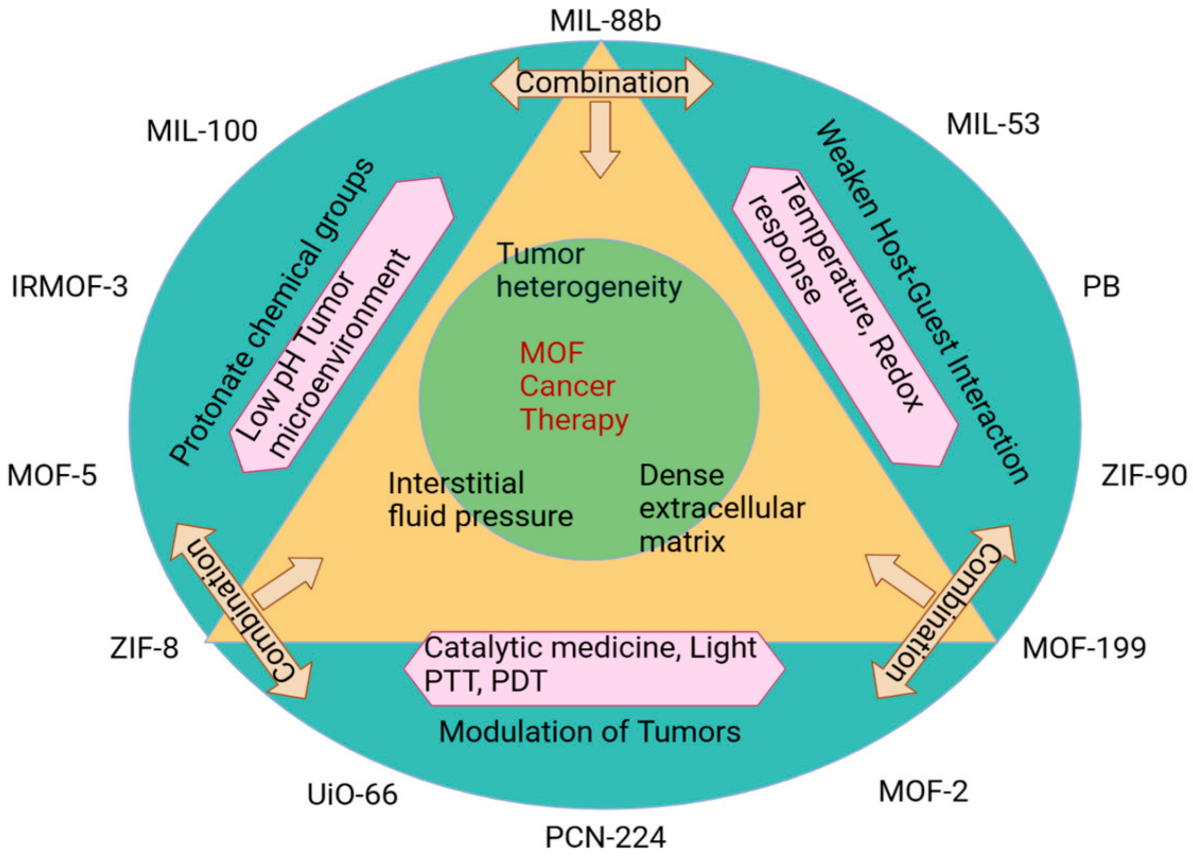

Figure 1. A MOF-based pH-sensitive vaccine delivery method for cancer MIL (Material Institute Lavoisier), IRMOF (Isoreticular Metal–Organic Framework), MOF (Metal Organic Framework), ZIF (Zinc Imidazole Framework), UiO

(Universitetet i Oslo), PCN (Porous Coordination Network), PB (Lead), PTT (Photothermal Therapy), and PDT (Photodynamic Therapy).

With an acid-labile chemical structure, pH responsiveness may be easily and quickly created. More pH-labile chemical structures, such as the reversible link generated by maleic anhydride and primary amine [10], may increase the efficiency of cross-presentation to the library of sensitive biomaterials. In addition to the most often investigated biomaterials, hydrogels and microneedles may potentially be employed for vaccinations against cancer that respond to changes in pH [11][12].

2. Acid-Triggered Phase Transition-Based pH-Responsive Biomaterials

Using charged peptides and polycarboxylic acids, which are non-degradable pH-responsive biomaterials, is also widespread in vaccine administration. After protonation, the biomaterials' increased hydrophobicity causes a considerable phase shift in acidic conditions. Hydrophobic interactions between the phospholipid hydrophobic domain and the protonated polymers may let vaccine components leave the endosome more easily [13].

Stayton and associates looked into several polymers with carboxyl groups for their use in the administration of vaccines. This group's model antigen poly (propyl acrylic acid) combination greatly increased the proliferation and survival of mice with tumors containing the EG.7-OVA gene [14]. As part of their distribution strategy, they employed amphiphilic block copolymers [15][16]. Due to their simple chemical production, for the administration of pH-sensitive vaccines, a wide variety of biomaterials having the property of acid-triggered phase transition have been produced. There is no assurance that the antigens and adjuvants contained in vaccination carriers will be released even if they undergo a phase shift. A disulfide bond, for example, may be added to this biomaterial to speed up when vaccine components are released from transporters after they enter the cytoplasm of an APC.

Phase transitions caused by pH have been mediated by biomaterials, improving cancer vaccine endosomal disruption and intracellular delivery [17][18]. These components are taken up and generate pore-like membrane structures by acidic endosomes because of their secondary and primary structure interactions. Yuba et al.'s pH-responsive fusogenic polymers [19][20] are examples of liposome-based vaccine delivery methods. pH-responsive liposomes have been used to construct a range of medicinal carriers, including cancer vaccines using synthetic mutagens with a comparable phase transition property [2]. Using a synthetic peptide rich in amino acids GALA (glutamic acid–alanine–leucine–alanine) [21][22], Morishita and colleagues described the surface conjugation of exosomes derived from mouse B16F10 tumors. MHC Class I antigen presentation was greatly improved by GALA-exo compared to that of unmodified exosomes. Liposomes are generally better than nanoparticles when it comes to the hydrophilic virus-specific loading capacity and vaccine cargo release speed (NPs). pH-responsive liposomes may have substantial limits since their lipid membranes are more vulnerable to rupture when injected intravenously with cancer vaccinations. By connecting the lipid bilayer, it is possible to stabilize lipid nanoparticle vaccines without affecting their ability to release antigens [23].

Natural and synthetic vaccine delivery techniques might benefit from the use of fusogenic peptides or polymers. If a vaccine, such as the one generated by Qiu et al., is self-assembled, it is possible to attach a pH-sensitive peptide (pHLIPs) to its surface to facilitate endosomal escape. They have an improved capacity to activate and proliferate antigen-specific T lymphocytes if loaded with an antigen such as NY-ESO-1 (NP-pHLIP) [24][25].

3. pH-Responsive Biomaterials for "Proton Sponge" Effect

Because of the low pH of endosomes, it is important to utilize polycations as buffers because of the high amine group count. For the delivery of nucleic acid payloads, the "proton sponge effect," which has been widely investigated and analyzed for its probable applicability, may be used. Methods such as these may help cancer vaccines escape endosomes. Tertiary-amine copolymer-based NPs (UPS) may be activated and deactivated in a very limited pH range (a pH change of 0.25) by Gao and colleagues [26]. Because of its potential to trigger CD8+ T cell responses, UPS NP PC7A was shown to be a promising carrier for cancer vaccination. Antigen carrier PC7A NP is also an adjuvant in this vaccine formulation, which shows STING-dependent DC activation. Administering PC7A as a cancer vaccine in mice prevents a wide range of cancers, including melanoma and colorectal cancers, from forming.

4. Other pH-Responsive Biomaterials

When it comes to cancer vaccines, the notion of integrating a pH-responsive promoter in addition to the other vaccine components is novel. Liu and colleagues confirmed this point by encasing the ammonium bicarbonate (NH_4HCO_3) activator and the vaccination payload in a thin-shelled PLGA NP (poly (lactic-co-glycolic-acid) nanoparticles) [27]. When NH_4HCO_3 reacted with protons in endosomes, they shattered the NPs' outer shell, allowing antigens to escape. The co-encapsulation of pH-responsive promoters and antigen distribution control is used in this method.

An investigation of the possible deleterious effects of intracellular CO_2 and NH_3 on cells is needed to understand how these gases disturb endosomes.

A considerable amount of work has gone into developing pH-sensitive biomaterials with a wide range of chemical structures for the delivery of responsive cancer vaccines. These biomaterials must be very sensitive to pH changes to fall into this specific category (from 7 to 5).

UPS NPs, which are very pH-sensitive, may promote anticancer effectiveness, as seen by an increased CD8+ T cell response. Improved pH-responsive biomaterial sensitivity is required for more effective cancer vaccinations, and this can only be accomplished by more accurately controlling antigen distribution. An efficient and reproducible preparation method is essential in the medicinal use of biomaterials. Studies in the therapeutic setting are more likely to focus on large-scale materials that have a reliable preparation procedure.

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