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Hypothesis Open Access

T Cell-Dependent *in situ* Initiation and Systemic Regulation Model of Immune Responses

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Hypothesis

A peripheral initiation and systemic response model of immunity. Very few antigen presenting cells (APCs) are able to elicit an immune response. We suggest, that peripheral immune activation, e.g. *via* the skin, may induce parallel co-migration of dendritic cells (DC's) and activated antigen-specific T cells to the draining lymph nodes and beyond. Herewith, memory-like anti-foreign-reactive T cells in addition or even superior to naïve T cells once co-migrating to the regional lymph nodes will immediately find optimal stimulatory conditions to fight systemic spread of infection. Yet, due to lack of local epithelial-specific antigen in the SLO's, this migratory pattern may help to avoid auto-reactivity in the case of an ongoing productive, and thus massively proliferating immune response involving all kinds of lymphocytes and other cells.

Background

Here, we propose, that even more than so far anticipated the most significant aspects in the initiation of immune activation as well as tolerance induction may directly and primarily take place at the local tissue level. And, thus, may initiate and result in the migration not only of maturating dendritic cells transporting and presenting antigen (DC's), but as well of significant numbers of activated antigen-specific T cells to the draining LN's and beyond.

Herewith, local antigen-induced anti-foreign reactive T cells in addition or even superior to naïve T cells once co-migrating to the regional lymph nodes will immediately find their cognate antigen plus optimal stimulatory conditions to further elicit immune responses.

This may save time especially in the case of an ongoing infection and may well include the activation or re-stimulation of tissue-resident and of migrating effector memory into a proliferative cell cycle, thus expanding and reaching the lymph nodes thereafter. As well as certainly inducing the differentiation of naive and central memory cells altering their survival and inducing a systemic migratory behaviour.

Yet, due to lack of local organ-specific self-antigen or generated neo-antigens reacting the LN's in the proliferative amplification of already pre-activated T cells in SLO's plus the lack of reactive cells due to a local immunosuppressive tissue-milieu, this activation and migratory pattern may help to activate against foreign, yet to avoid auto-reactivity in the case of an ongoing productive and thus massively proliferating immune response involving all kinds of lymphocytes and other cells.

Therefore, overall, we propose a not yet fully recognised vigorous interplay and a much neglected imprinting in the current pool of polyclonal T cells of the sum of antigen presented in total by which the primary and secondary lymphatic organs sense and respond to the current status of tertiary tissues and vice versa. Yet, the T cells may respond to every possible antigenic structure. So their potential.

In this sense, we moreover propose the significant tissue-derived antigen-specific "reverse regulation" of T cell selection, maturation and proliferation after activated T cells re-enter the thymus and the lymph nodes. Regulatory T cells generated in the thymus thus may merely represent a transient status of T cells generated by recognition of current thymus self-influenced by the current peripheral self. We see the rather strict separation into cellular regulatory and effector linages secondary to a gradual and reversible polarisation of activated immune cells. Importantly, we see the individual expanding and reacting and differentiated or polarised T cells and thus the total T cell reactivity initiating effector function as rather flexible.

In terms of antigen specificity, priming or vaccination induces the generation and survival of memory cells. Yet, the major force of antigen-specific action of effector memory as well as central memory cells maybe not be the altered reactivity towards the respective epitope and the corresponding epitope specific cell, yet the altered sum of *in vivo* reactivity to the sum of each of the respective exogenous or self-proteins in the respective organ context.

This overall may modify the way to judge and manipulate self-and non-self-reactivity in diverse settings of immune regulation including "danger".

Introduction of a Change of Theoretical Aspects of T cell Activation

T cell activation by dendritic or tissue cells leading to altered migration pattern supporting primary and secondary lymphatic organ re-entry

Very few antigen presenting cells (APCs) are able to induce protective immune responses. In addition, parenchymal antigen as tissue-specific and directly presented antigen may significantly stimulate T cells. Once these mostly CD44-high tissue-resident T cells have altered their immune status and have enter regional lymph nodes they may ad hoc exert their individual effector function, may continue to mature and expand rapidly. Additionally, they may then as well complement significantly to the novel priming of naïve T cells.

T cells are well known to relocate throughout the entire organism. Here, we additionally we wish to suggest that the functional relevance of T cell re-entry after antigen-specific stimulatory recognition of peripheral self-antigen into the thymic environment, e.g. of anti-epithelial autoreactive lymphocytes, has been by far underestimated. Theoretically, if the tissue itself holds the option to induce regulatory T

cells the relative need for thymus released regulatory cells may be limited, as may be seen and analyzed by the function of various regulatory populations considering different genetic backgrounds. Thus, the higher the relative capacity of the peripheral tissue to induce regulatory function, the stronger is the limitation of antigen-specific activity and the less peripheral "pressure" reaches the thymus and the lower is the need and the effective generation of Tregs in the thymus. This may be mechanistically and functionally relevant and may modify the induction of immune regulation via intra-thymic recognition and further induction of expressed cognate epithelial self-antigens. Overall, these may be thymically expressed in a more immature/embryo-like form and structure as compared to peripheral antigens.

First, ectodermal-specific/reactive thymocytes cells may accumulate and be positively selected in a strictly antigen-directed manner by ectodem-derived corticoepithelial (cTECs). Later entodermal-specific and derived medulloepithelial thymic stromal cells (mTECs) may induce regulatory function. Thus, we envision the later as the higher-possibly IFN gamma-mediated-inducers of AIRE and clusters of self-antigens, once they are recognized by antigen-specific thymocytes.

Thus, their specific mTEC-peptide-epitopes are combined with a predominant function in negative selection and tissue-specific Treg induction.

This may reflect the need for a more stringent protection of internal entero-dermal derived surface areas from auto-aggression. Peripheral tissue cells including exterior surfaces are increasingly recognized for their immune-modulatory as well as immune-stimulatory function. An acute viral infection, for instance, has been shown to activate significant numbers of CD8+ T cells including tissue-resident memory cells specific for non-viral epitopes. Yet, it remains unclear to which extent the various viral or organ self-epitopes of which cellular compartments and mechanisms like molecular mimicry, 'bystander activation' or further theoretical mechanisms play a role. As e.g. for peripheral effector T cells, e.g. after $Ca2^{+}$-release and IFN-gamma dependent stimulation and differentiation, we envision here for the intra-thymic migration-pattern as well for the re-entry, a significant role for surface molecules, including CCR7, CXCXR5, etc. As mentioned above, we see the main point of expressing and regulating the surface phenotype, e.g. CD44, CD69, CD127, CD69L, $S1PR1^{+}$, $KF2^{+}$, in a rather transient polarisation status.

Regional surface T cell activation may cause anti-epithelial auto-reactivity

Therefore, we wish to suggest that peripheral antigen recognition, e.g. in the skin, may lead to wanted anti-foreign, yet unwanted anti-epithelial T cell activation. Evidently, most infectious challenges will primarily initiate an immune response at the level of the entry site of the local inflammatory tissue milieu. These surface areas which serve as a barrier to the exterior are not yet seen as a lymphatic organ or as a prominent part of the immune system. Yet, the initial innate immune response will elicit and require an antigen-specific response, if the stimulatory epitopes plus the stimulatory conditions prevail. As the antigen-specific T cells have "preset" an extremely diverse antigenic repertoire, this initial activation phase-as we wish to propose and discuss-may well take place at the tertiary tissue level. And only the rather secondary amplification of the peripherally induced priming of a novel immune response moves to the draining local lymph nodes, including activated dendritic cells, yet may-as we wish to suggest - include parallel migration of activated T cells as well as these will be ad hoc expandable: pre-activated DC's plus the respective matching pre-activated T cells. Yet, due to lack of local epithelial-specific antigen in the SLO's, this migratory pattern may help to avoid auto-reactivity in the case of an ongoing productive, and thus massively proliferating immune response involving all kinds of lymphocytes and other cells. For this event initially very few antigen-specific T cells may be sufficient. As surface areas may elicit anti-epithelial reactivity, this antigen specificity will be spared, once these T cells move to the mesenchymal-derived medullary region of the local lymph node. In the embryo, the thymus is known to develop from an endodermal pouch and an ectodermal cleft. Intense proliferation of the ectoderm of the third cleft covers the endodermal part. Thus, the thymus holds a central endodermal part and a peripheral ectodermal region, therefore the cortical cells being ectodermal, and the medullary cells endodermal in origin. As described above, this may be of functional relevance.

So for both, the T cells gaining a tolerazing as well a activation signal the tissue contact may be of central importance by reversely regulating thymus positive, negative selection plus the induction of regulatory T cells.