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Rorschach's Immunology: The Hematopoetic Cells

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The B cell is personified into an entity aware of his individuality but lacking free will; once divested of his appointment in the immune system, the afterlife grants him understanding of the toils of his earthly life.

The Bends

You should know: you are going to change.

It is not supposed to mutilate,
It is not supposed to hurt;
It is neither a punishment nor a reward.

You exist by rote, by default.
Your evolution is both crude and refined,
Bizarre and sensible, and
As random and perfect as the distance between raindrops.
To you, both beauty and apathy aspire.

The insults and their void, chances and probabilities of this maze
Have served, seasoned, proofed, and kneaded you,
Until you overshadowed the naïve, impractical grain you started as
With a conniving collection of mature, serviceable flecks.

You have lost yourself
To this swarm of others you inspired—
They claim your history, personality, morals,
Your limitations, and inclinations.
For all their fawn, they reject your subtleties for their own.

You watch them evangelize with upward inflection,
Their amulet a crotch angle bisected on the convex.

Incidentally, you know who the real prophets are,
And you never wondered ‘*why me*’—
You already knew

Editorial Commentary

The “bends” are the contours of the endoplasmic reticulum of a plasma cell as it churns out antibodies to fight an infection, or “insult.” “The bends” is also a reference to the disabling and potentially lethal state that results from an insufficient immune reaction.

The “change” is the reinvention of the B cell through its development: from its initial differentiation in the bone marrow, to circulation to the secondary lymphoid structures (the lymph nodes, the spleen, the tonsils, the MALT and GALT), to its meeting an antigen—which may not even happen. The end goal of a B cell (at least a B-2 cell, which comes into existence after birth) is to become a source of “amulets”—Y-shaped antibodies called upon to thwart a specific pathogen by physically blocking its mode of action; holding it in an environment where the body can easily get rid of it (as in the mucosal tissues with IgA); targeting the activation of complement on it (in the case of pentameric IgM); and generally inhibiting its pathogenic activity.

While still in the bone marrow, the B cell’s genetic constitution is jumbled up in an effort to create a usable B-cell-receptor (membrane bound form: immunoglobulin, soluble form created by alternate splicing of RNA: antibody). The gene rearrangement process is called V(D)J recombination, and is facilitated by the RAG1 and 2 enzymes, present in all jawed vertebrates. RAG has the capacity to select one from a cluster of each of the variable, diversity, and joining gene segments to produce the heavy chain (longer side) of the B-cell-receptor. In the successful version of the story, this “mu” heavy chain is made from genes on one of the two homologous chromosomes in the cell and is able to bind to a surrogate light chain, reinitiating the expression of RAG to combine one of each of the variable and joining segments to make a light chain of either the kappa or lambda variety. The receptor is self-tolerant, meaning it dismisses antigens that are natural constituents of a healthy body, but affixes itself to antigens that are foreign. The B cell then leaves the bone marrow in search of its antigen.

If the mu chain is nonfunctional or cannot bind to the surrogate, or if the receptor binds to multivalent self antigens in the bone marrow and does not edit away the issue on the light chain, it dies by apoptosis without ever seeing the rest of the body. If it binds to monovalent self antigens in the periphery, it will be rendered anergic: stunted in its lifespan and ability to be activated (proliferate and differentiate further). There are many opportunities to fail as a B cell, but with 2.5 billion being made daily, the consequences of individual failures are slight.

Even with a quality receptor, the B cell is not guaranteed to encounter the antigen it is specific to. B cells regularly check follicular dendritic cells in the secondary lymphoid

organs for an antigenic match. If the antigen is not found within a certain timeframe, the B cell dies by apoptosis.

If the B cell does bind to the follicular dendritic cell, it “matures,” receiving survival signals. It will be prompted to find its follicular helper T cell mate in the secondary lymphoid tissue that shares that antigen specificity. Together they will proliferate, making a “swarm” of “flecks,” and each generation will sustain a rate of hypermutation otherwise frowned upon in the biological arena. To make antibodies, isotype switching at the switch region of the immunoglobulin modifies and effectively beheads the portion of the constant region that allows for attachment at the cell membrane. Signals from the T cell decide which isotype is made. Some of the B cell progeny are directed to plasma cell-hood (as rendered in the painting) to acutely suppress the infection; the best and most affinity-matured specimens will be memory cells, summoned upon re-infection with the same pathogen.

At this point, the prognosis of a cleared infection is promising. But amidst the chaos of heavily mutated semi-conservative cell replication, with no questions asked, the individual B cell from which all these iterations descended has ceased to exist.



A comment on environmentalism, echoing the macrophage, which, unlike humanity, sees and protects the whole system instead of just itself.

How Atlas Lost the Earth

At first, it was a scene of mass cooperation—
People quixotically agreed
To dismantle the obsolete symbol of human dominion.

Each one cast their line, and pulled,
But Earth didn't rock:
The force came evenly from all angles.

The people shrugged—of course.
It was too grand an artifice anyway.

So they let it alone.
They inhaled the spoils
Of their unbecoming,
Externalized collateral waste,
And Atlas quietly, decidedly,
Fell off the map.

Editorial Commentary

This lofty, rather inconsequential idea to pull the Earth off Atlas's shoulders is dismissed too easily—like the highly consequential idea to moderate the human impact on the environment.

One source of the impact is wastefulness and waste created by “the artifice”—society's technology and the (non-Greek) myth that “it's not my problem.” It just so happens that the image of a macrophage under scanning electron microscope (SEM) resembles a sphere tethered everywhere by ropes. Incidentally, macrophages selflessly clean up all the waste created by the system they are a part of. They don't create all the dead, dying, invasive, or mishappen figures they dispose of, but they assume responsibility anyway, because it's their God-given nature to do so, and it ensures their environment is healthy. Humans don't need to be so selfless about it, because in our case, we do create the waste that needs proper disposal. But, we submit to the inclination to act in favor of short-term personal gain and the inclination to ignore long-term collective detriment. In light of this, Atlas fell off the map in two ways: people gave up on him, and he (a projection of human

consciousness) was so dismayed that he gave up holding the Earth (just as humans give up an ethic of environmentalism).

Macrophages are widely distributed within the body. They are phagocytic cells, but are not the single-use disposable kind that neutrophils are. Instead, they live longer, are professional antigen presenting cells, and create inflammation.

A natural infection is the initial signal for inflammation. Components of bacteria (like lipopolysaccharide, teichoic acid, DNA fragments, and lipopeptides) or opsonins (like antibodies and complement) are detected through toll-like receptors (extracellular) or NOD-like receptors (intracellular) on macrophages. Complement is a protein made by the liver. From here, a kinase cascade dissociates the transcription factor NF κ B from its inhibitor, allowing it to move to the nucleus and increase the rate of transcription of genes for inflammatory cytokines. When the activation of NF κ B is inhibited, macrophages cannot communicate via cytokines to the rest of the body, and individuals are more susceptible to bacterial infections. This occurs in X-linked disease NEMO deficiency.

Among the inflammatory cytokines are IL-1 β , IL-6, IL-12, CXCL8, and TNF α . The tissue dilates and becomes molecularly sticky, in preparation for an influx of neutrophils, monocytes, and natural killer cells to enter infected tissue and get the infection under control. Under these cytokines, monocytes mature into new macrophages; natural killer cells also mature. Pyrogens create fever, imposing sluggishness upon bacterial metabolism and reproduction. T_H1 and CD8 T cells synapse with macrophages to augment their performance: after a few hours of signaling, the macrophage's phagosome is more toxic and fuses more efficiently with the lysosome.

When these cytokines reach the liver, they instruct it to reappportion the concentrations of various blood proteins, called acute-phase proteins (corresponding to the acute phase of the infection). C-reactive protein, a pentameric, radially symmetrical specimen, binds to bacteria, fungi, and some parasites, on which it can initiate the classical pathway of complement activation. Mannose-binding lectin binds to pathogens and initiates the lectin pathway of complement activation. Serum amyloid A causes positive feedback of inflammatory cytokine production.

Macrophages specialize depending on the region of the body they occupy. For example, Kupffer cells in the liver and alveolar macrophages in the lungs are subjected to the commensals of the gut and pollutants of the air, respectively.

Mucosal tissue (gut and respiratory) is much more of a microorganism hot-spot than non-mucosal tissue. Intestinal macrophages lack the receptors that allow them to produce inflammation and activate T cells. Inflammation would allow commensals out of the gut,

where they are indispensable to health, and into the bloodstream, where they are destructive to health.

Macrophages are also resident in the secondary lymphoid organs. Tingible body macrophages are located in the germinal centers of proliferating B cells, and phagocytose cells that fail to receive survival signals. Subcapsular sinus macrophages are nontraditional in that they do not phagocytose, but use complement receptors catch incoming pathogens from the afferent lymph, relaying them to follicular dendritic cells to display to B cells that are maturing. Medullary sinus macrophages resume the habit of phagocytosis, preventing blood-borne infection by catching any bacteria that were missed by the subcapsular sinus macrophages before exiting the lymphoid tissue.

At every stage of B and T cell development, cells that lack a serviceable receptor render themselves apoptotic. Macrophages in the bone marrow and thymus dispose of these cells. Macrophages are also there for apoptotic cells of all other types in all other organs and tissues, keeping the living body relatively free of decaying clutter.