How B-Cells Work & Talk to Each Other

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How do B-Cells Work?



How do B-Cells Work? Lymphocytes to Plasma cells to Antibodies









How do B-Cells Work? Lymphocytes to plasma cells to antibodies – the B-cell receptor pathway



How do B-Cells Work? Lymphocytes to plasma cells to antibodies – the Toll-like receptor pathway



How do B-Cells Work? Various types of Immunoglobulins

Characteristics	lgG	IgM	IgA	lgD	IgE
Structure	Monomer	Disulfide bond J chain Pentamer	J chain J chain Secretory component Dimer (with	Monomer	Monomer
			secretory component)		
Percentage of Total Serum Antibody	80%	5-10%	10-15%*	0.2%	0.002%
Location	Blood, lymph, intestine	Blood, lymph, B cell surface (as monomer)	Secretions (tears, saliva, mucus, intestine, milk), blood, lymph	B cell surface, blood, lymph	Bound to mast and basophil cells throughout body, blood

What went wrong in Waldenström macroglobulinemia?

- Lymphoplasmacytic infiltrate
- IgM protein
- Anemia, lymphadenopathy, hyperviscosity



Problem 1: The monoclonal protein

- The protein in WM is IgM, not IgG
- The protein molecules are all identical
- The protein production appears
 poorly controlled
- High IgM levels can result in clinical symptoms



Problem 2: The malignant lymphoplasmacytic cell

- Lymphoplasmacytic lymphoma involving either the bone marrow or extramedullary sites
- Cytologic spectrum small lymphocytes to well-formed plasma cells
- High levels of surface CD19, CD20, and immunoglobulin light chain expression



What causes the increased production of IgM in Waldenström macroglobulinemia?





How do B-Cells Talk to Each Other?

Just as with people, effective communication between cells is very important to effectively get a task done.



B-cells communicate by cytokine, chemokine, receptor/ligand interactions



Some interactions are local – the message is only heard by cells nearby



Some interactions require cell contact –

cells need to physically touch each other



Some communication is more long distance –

the message is sent by cells that are not in the immediate neighborhood



Sometime cells are told to do things they shouldn't



Cytokines are elevated in WM – Told to do too much



 Cytokines are proteins to allow cells to communicate They are secreted after stimulation •They play a role in many cell responses They often affect the actions of other cytokines

Cytokines are elevated in WM



B-lymphocyte stimulator (BLyS)

- Critical for maintaining normal B-cells and for immunoglobulin production
- Too little BLyS results in absence of Blymphocytes and low immunoglobulin levels
- Too much BLyS in mice causes lymphoma

BLyS expression in WM





WM 8

NBM

BLyS increases IgM in WM cells



Where does BLyS come from? **Autocrine Paracrine** BCMA **APRIL** BAFF-R TACI BLyS NF-kB **APRIL** Bax Bcl-2 Bim Bcl-xL **BLyS Tumor Environment**

Malignant B cell

BLyS collaborates with other cytokines including IL-6 and IL-21 to produce IgM



IL-6 expression increased in WM

- Inflammatory cytokine
- Causes B-lymphocyte proliferation and differentiation
- Stimulates T-cell proliferation
- Serum levels are elevated in WM patients



IL-6 increases IgM levels in WM

- Increasing amounts of IL-6 increases IgM production
- IL-6 is controlled by a different cytokine - CCL5



IL-21 expression increased in WM



- IL-21 produced by T-cells and NK cells
- Promotes plasma cell growth
- Prevents death of cancer cells



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IL-21 controls plasmacytic differentiation and IL-6 production



CCL5 (Rantes) controls IL-6 in WM

- CCL5 levels are very high in patients with high IgM levels
- CCL5 is produced by WM cells
- Signals through a intracellular protein GLI2



Sometimes the instructions to cells are very "loud"



MYD88 Mutations amplify the "Communication"



Expression of Pro-Survival Genes and Cvtokines

The role of cytokines and immune ligands in controlling IgM levels in WM



Summary

- Waldenström macroglobulinemia is a disease with two problems – the cancerous cell in the bone marrow or lymph nodes and the protein in the blood.
- Cytokines made by cells in the tumor microenvironment support the growth of the cancer cell and the production of IgM.
- IgM is controlled by cytokines including BLyS, IL-6, IL-21 and CCL5. Interfering with this control may be a future treatment option.

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