



Microenvironment and B-cell lymphoma

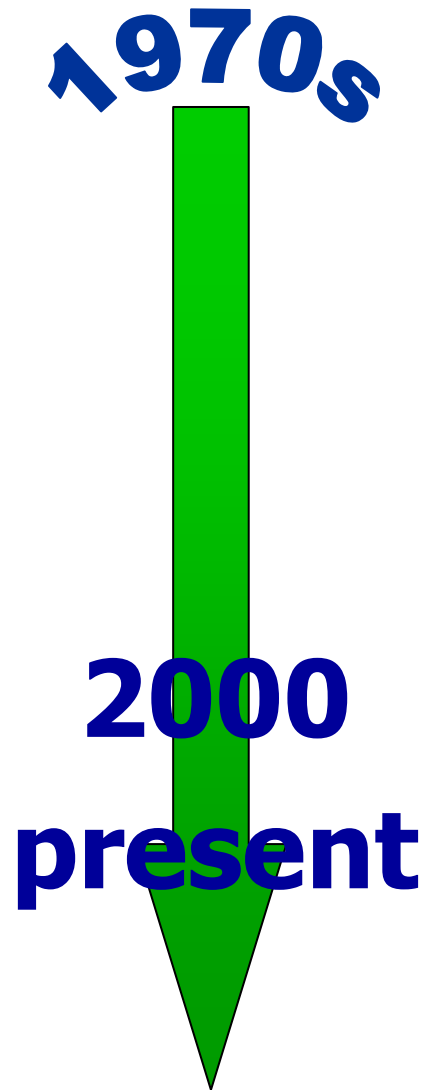
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XIV EAHP meeting, Bordeaux 2008

From a genetic disease to a complex signaling network

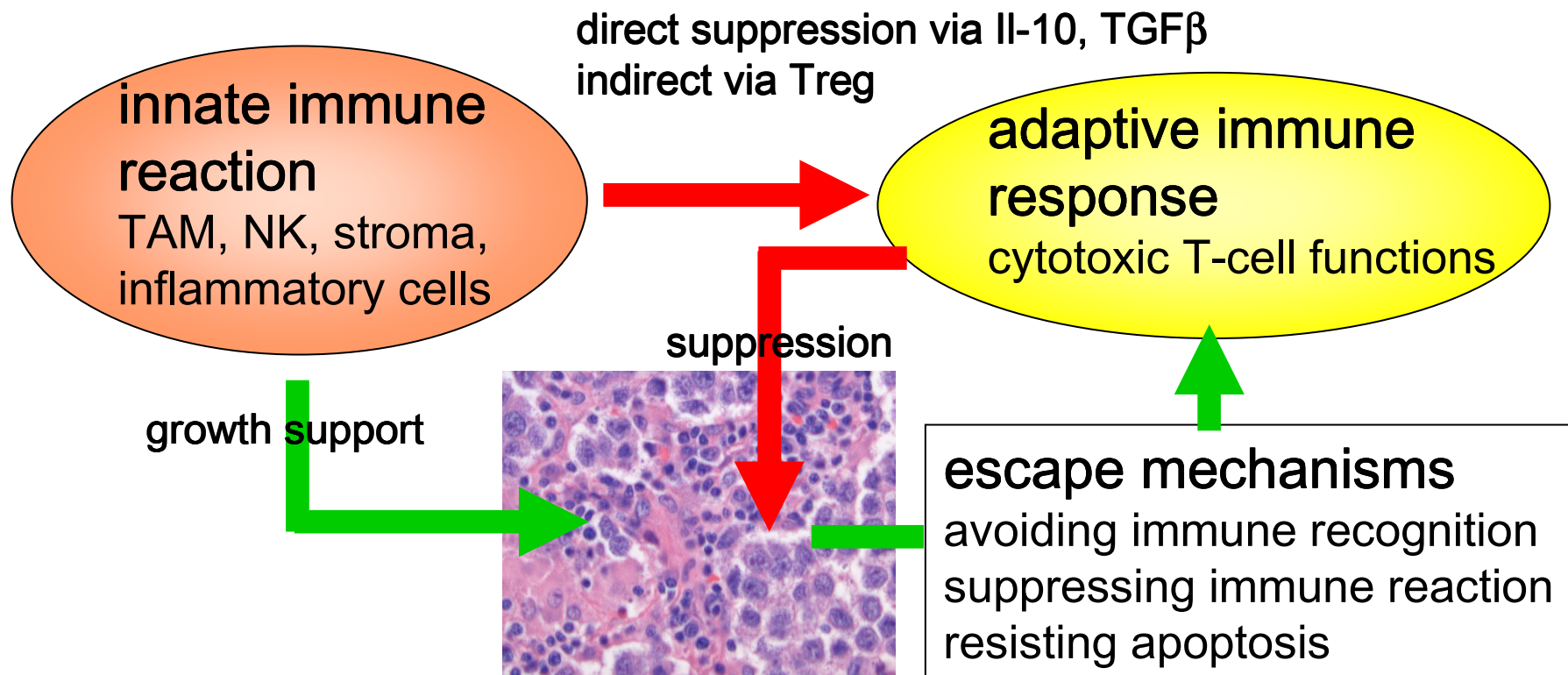


- most human cancers arise by mutations in growth controlling genes
- tumor formation is the result of multiple sequential genetic alterations
- tumor microenvironment infers cytotoxicity and the tumor cells develop escape mechanisms
- tumor microenvironment delivers tumor-promoting and growth – supportive signals
- tumor microenvironment as a primary target for therapy

Mechanisms by which immune cells regulate cancer development

- **Innate immune cells (tumor-infiltrating macrophages, granulocytes, eosinophils, mast cells)**
 - DNA damage by free radicals
 - Paracrine regulation of intracellular pathways (NFkB)
 - Promotion of angiogenesis, production of growth factors, cytokines, chemokines
 - Suppression of an antitumor adaptive immune response
- **Adaptive immune cells**
 - Inhibition of growth by cytotoxic T-cell response
 - Inhibition of cytokine-mediate tumor cell lysis
 - Growth support via suppression of cytotoxic response by Tregs
 - Growth support by humoral immune response and induction of inflammatory response

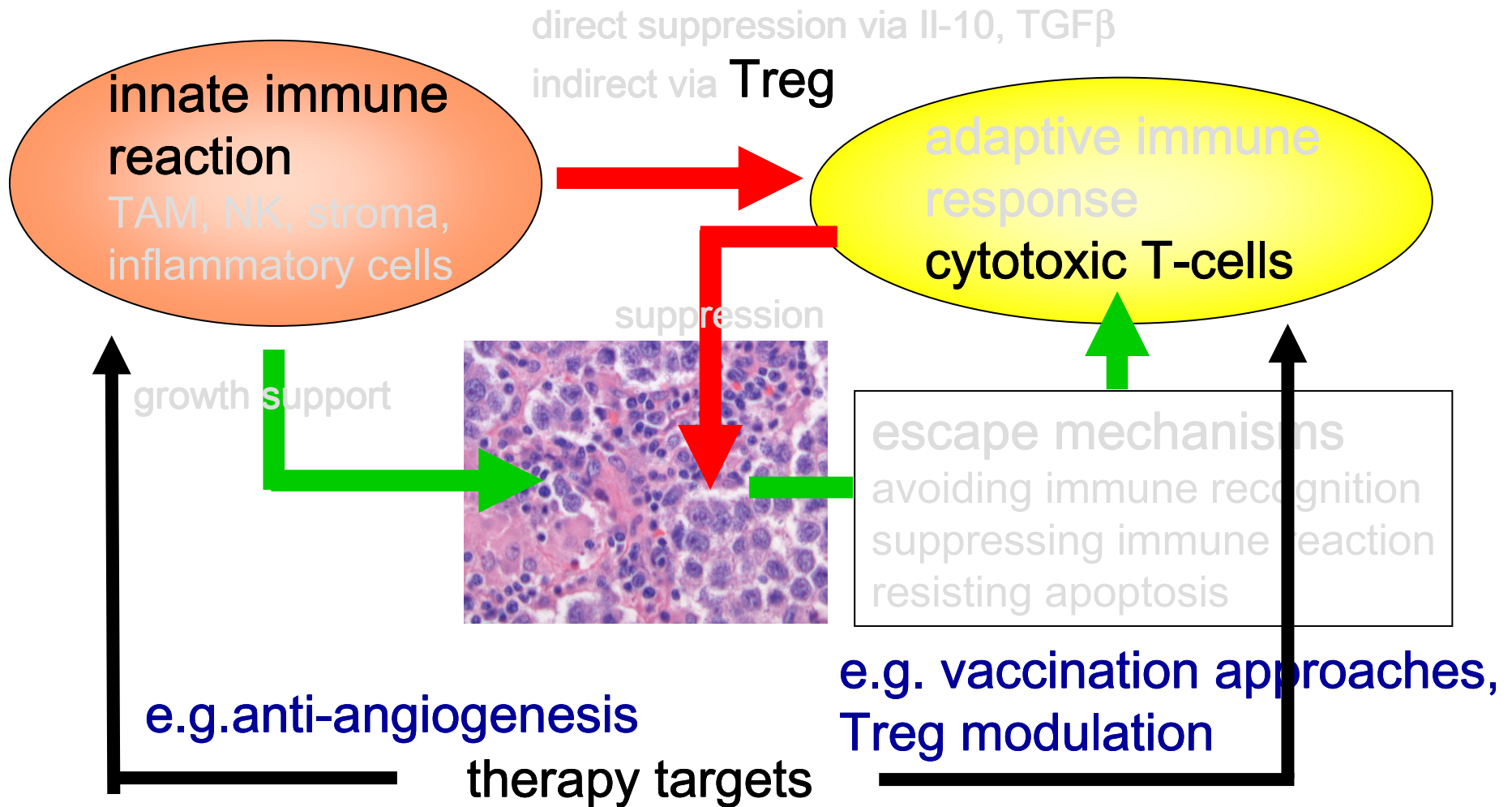
The role of the immune microenvironment in carcinoma



Prognostic impact of the immune microenvironment in carcinoma

- **Good prognosis**
- Dense infiltrates of NK cells in gastric and colon cancer
- **Poor prognosis**
- Dense infiltrates of macrophages in breast cancer
- Dense infiltrates of mast cells in lung cancer and melanoma
- Dense infiltrates of Tregs in many cancers

Immunotherapy in carcinoma

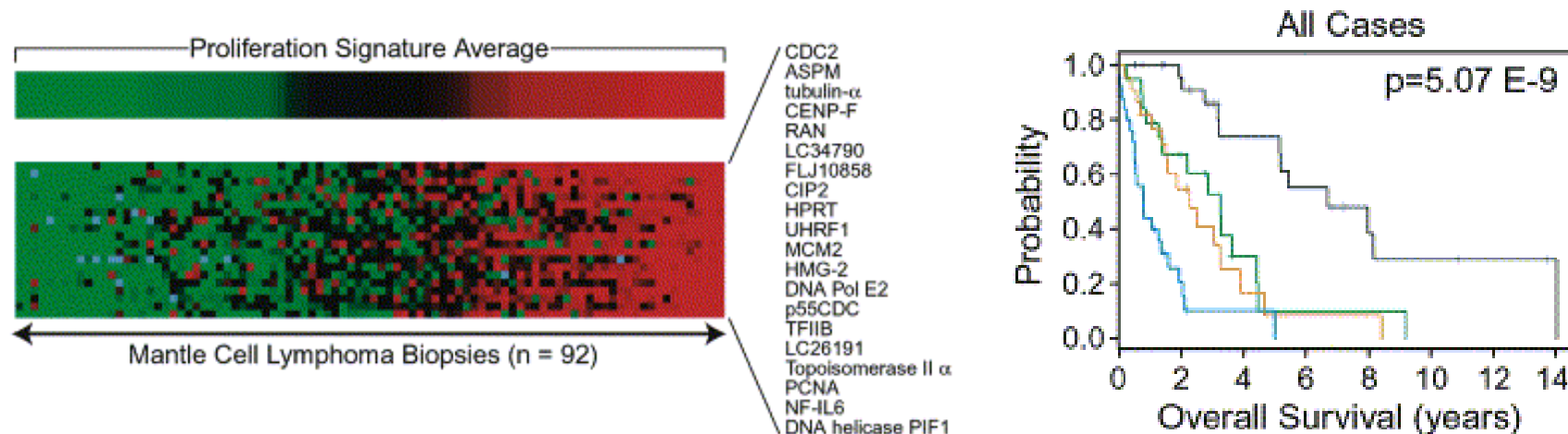


Essential difference between carcinoma and B-cell lymphoma

- Malignant B-cells are still **professional immune cells**, that are regulated within immune networks
- **Levels of regulation differ between lymphoma subtypes**
 - Burkitt lymphoma and mantle cell almost completely genetically driven by interference with cell cycle regulation
 - Marginal zone lymphoma, MALT-type predominantly driven by infectious factors
- **Role and direction** of the immune microenvironment in tumor behavior and impact for prognosis differs between (and within) lymphoma subtypes

Immune microenvironment in MCL

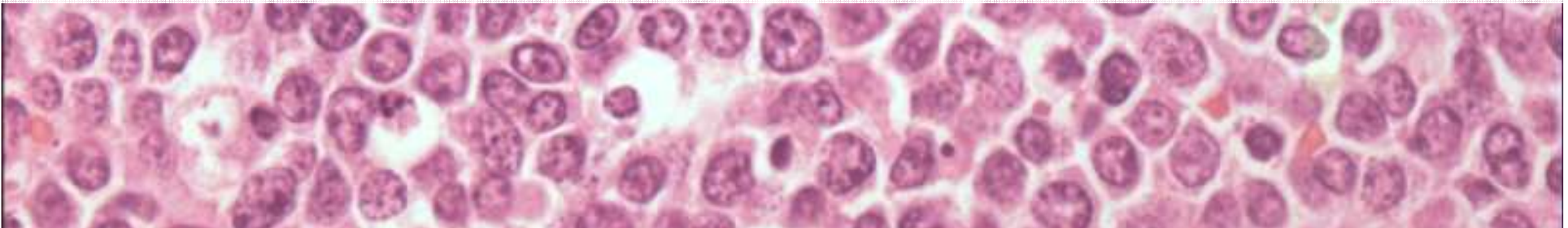
- T-cell and accessory cell components are mostly sparse
- Prognostic gene-expression signatures are dominated by proliferative tumor cell information
- Microenvironment plays a minor role



Rosenwald et al. *Cancer Cell*. 2003;3:185-97, Kienle et al. *Clin Oncol*. 2007;25:2770-7, Salaverria et al *Clin Oncol*. 2007;25:1216-22

Immune microenvironment in BL

- BL is principally driven by proliferation balanced by apoptosis
- Innate immune response may play a role via macrophage dependent apoptosis protection and survival support
 - In vitro survival support by activated macrophages via Il-4, Il-10, TNF α and BAFF
- Contribution of T-cell populations is rather unclear

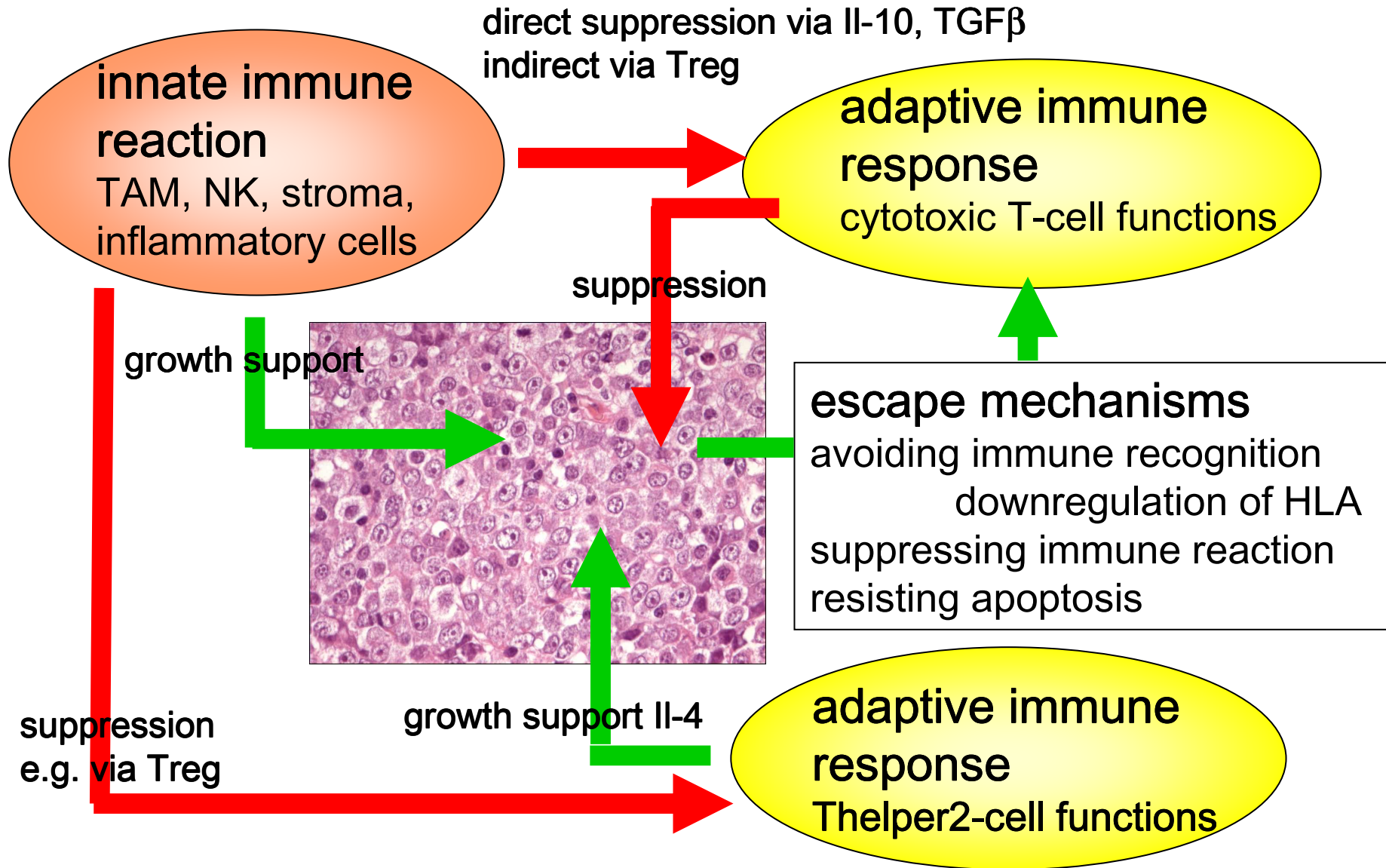


Heterogeneity in DLBCL

- **Component of non-malignant infiltrate is variable**
T-cell / histiocyte rich B-cell lymphoma
- **Biological subtypes**, defined by “BCR/proliferation”, “OxPhos” and “host response (HR)” independent of “cell of origin”
- HR made up of activated T/NK cells, macrophages, (S100+) dendritic cells, stromal cells
- Function may be either growth supportive or cytotoxic (or both)

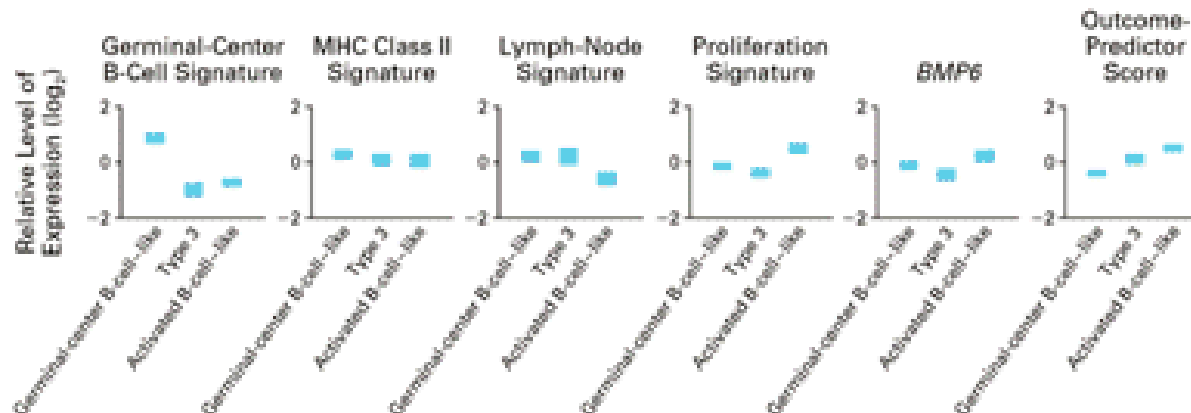
		Consensus clusters			
		OxPhos	BCR/ Prolif.	HR	CTOT
COO	ABC	9	18	8	35
	GCB	23	41	15	79
	Other	18	18	26	62
	RTOT	50	77	49	176

immune microenvironment in DLBCL



Extrapolate the function of the immune microenvironment from prognostic impact

- Gene-expression studies
 - Distinction between ABC/GCB subtypes based on functional gene clusters, including “lymph node signature”
 - lymph node signature contains macrophage and matrix information and is correlated with favorable prognosis, suggesting a cytotoxic response



Rosenwald et al.
NEJM 2002; 25: 1937

Extrapolate the function of the immune microenvironment from prognostic impact

- Immunohistochemical studies

- good prognosis

- S100/CD1a+ IDC
 - dense cytotoxic T-cell infiltrate
 - dense mast cell infiltrate
 - presence of CD21+ FDC
 - dense FoxP3+ Treg
 - TAM content (as suggested by GEP) dubious



effective
cytotoxic
response

Extrapolate the function of the immune microenvironment from prognostic impact

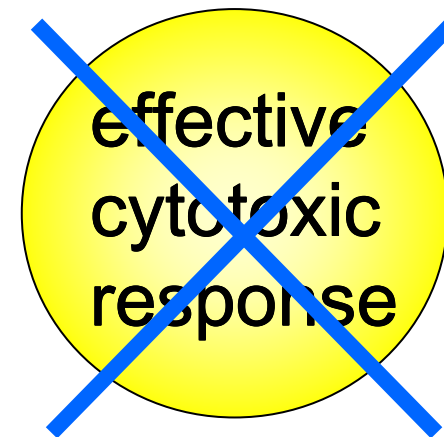
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- poor prognosis

- dense cytotoxic T-cell infiltrate
- dense FoxP3+ Treg



immune escape in DLBCL

Lack of MHC expression on tumor cells

- homozygous deletion
- transcriptional downregulation +/- heterozygous deletion
- correlated with fewer cytotoxic T-cells
- correlated with poor survival



effective
immune
escape

immune escape in DLBCL

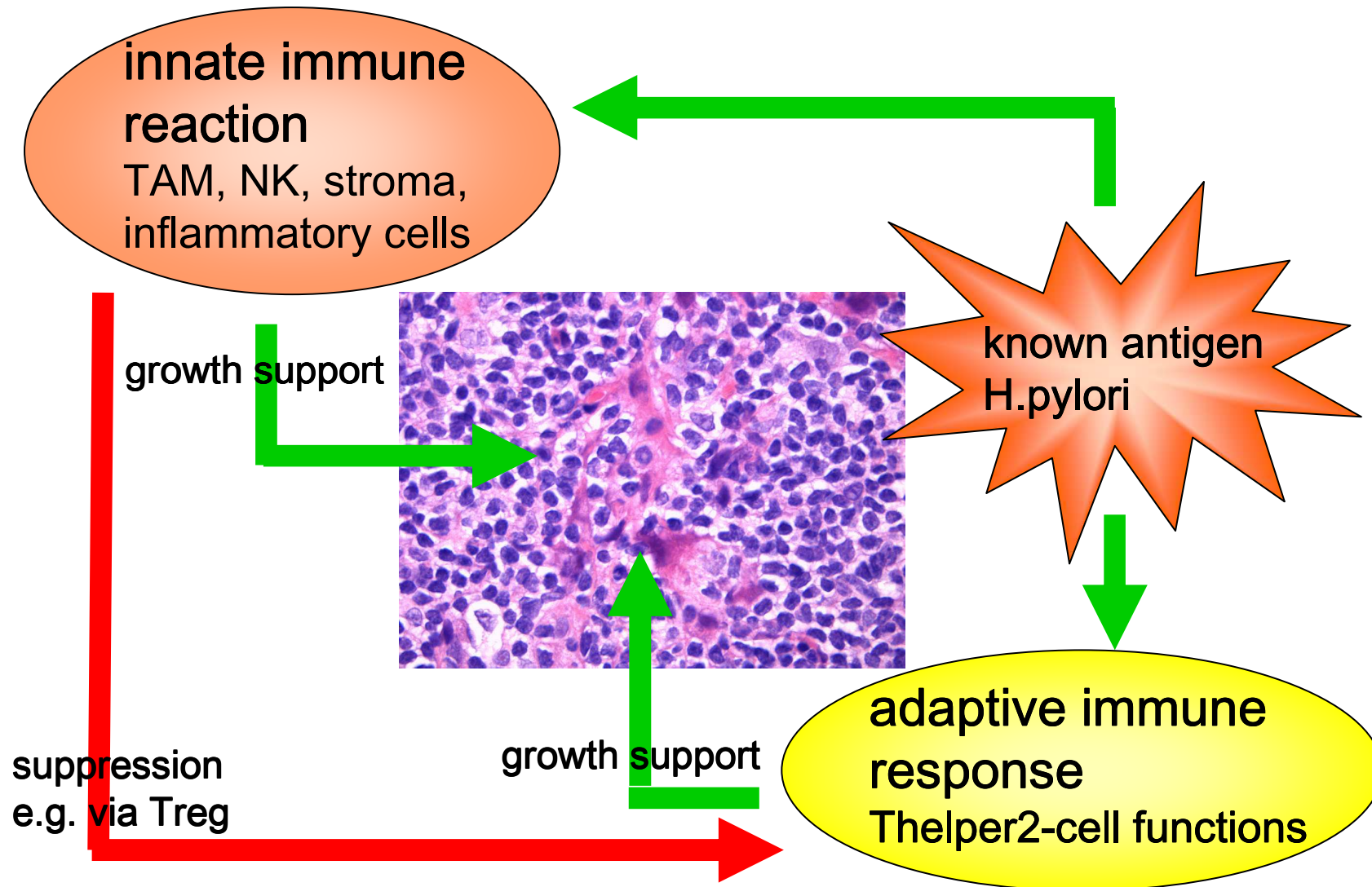
Disruption of apoptosis response

- defects in caspase 8 mediated pathways is related to treatment resistance and poor prognosis
- defects in caspase 9 mediated pathways exert similar effects



effective
apoptosis
resistance

MALT lymphoma as a predominantly immune driven disease



composition and function of the immune microenvironment in MALT lymphoma

- deceptively few studies
- In vitro evidence for autologous T-cell growth support
- no difference in composition and density of T-cell populations and TAM in relation to response or translocation status
- no differential response to fludarabine treatment

Consequences for treatment

- **Growth supporting and cytotoxic effects** of the innate and adaptive immune response are differently balanced in B-cell lymphoma
- Precise contributions and balances of non-malignant cell populations are insufficiently known
 - in vitro studies
 - correlative studies
- **Evidence-based targeted treatment designs** directed towards the microenvironment are still difficult, although empirical approaches can be highly effective
 - wipe it out? Which cell populations?
 - boost it? Which cell populations?