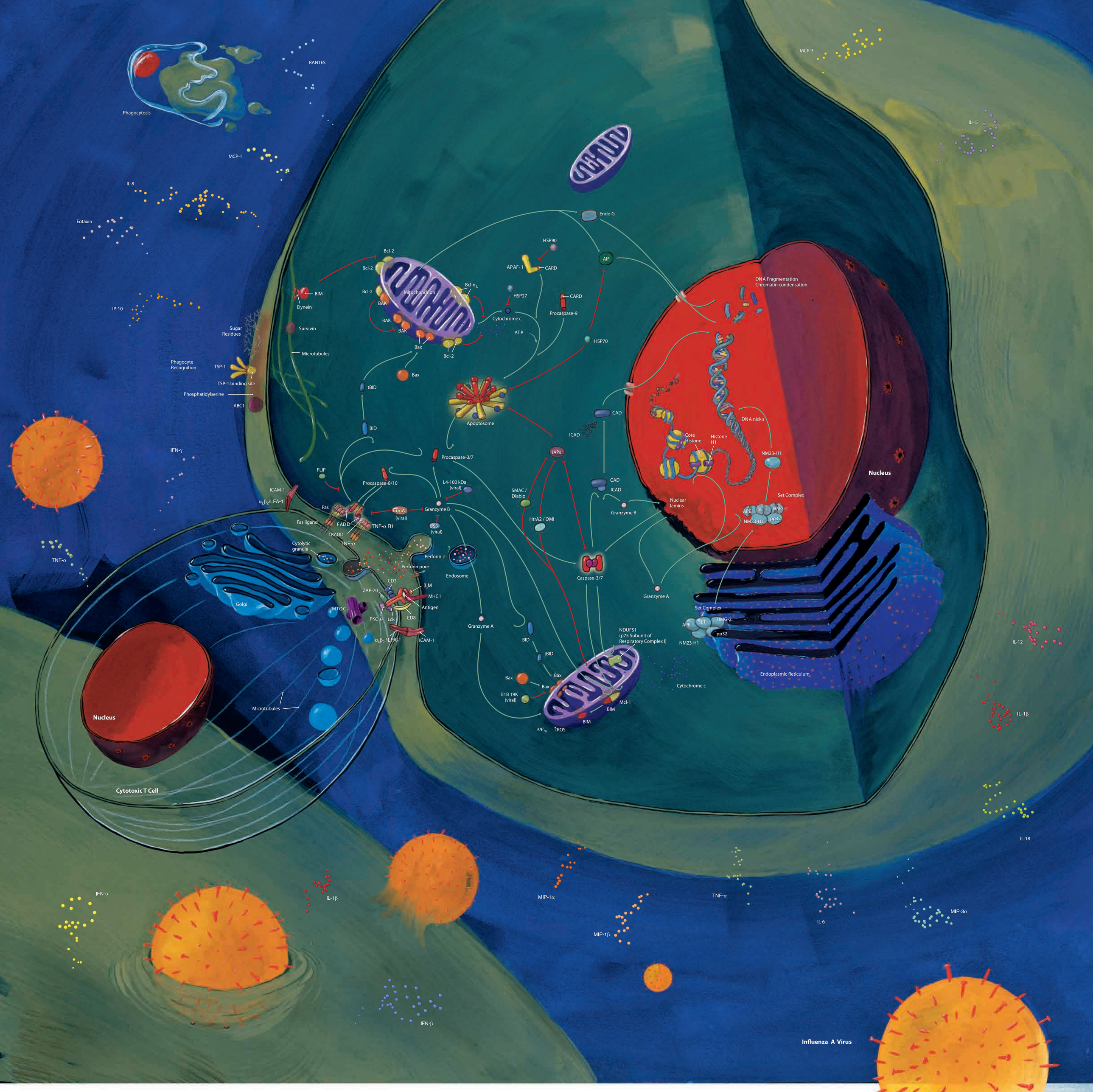

T Cell-mediated Cytotoxicity

Introduction

Cytotoxic T lymphocytes (CTLs) are an essential part of the adaptive immune response to viral infection. They can elicit apoptosis in the target cell either through the release of cytolytic granules, or through the ligation of TNF superfamily death receptors. CTLs recognize MHC I-associated antigen on target cells via a T cell receptor (TCR) complex that includes TCR, CD3, and CD8. Antigen recognition stimulates signaling cascades that reorient the Golgi and the microtubule-organizing center (MTOC) toward the target cell and cytolytic granules move toward the membrane for docking and release. The immunological synapse formed between a CTL and its target is stabilized by adhesion molecules including $\alpha_L\beta_2$/LFA-1 and ICAM-1. Key components of the granules include the Granzyme proteases and the membrane-perturbing protein Perforin. Classically, Perforin was thought to form pores in the target cell plasma membrane for passive diffusion of cytolytic molecules. More likely, the mechanism involves endocytosis and subsequent Perforin-mediated release from the endosomes.

Granzymes A and B, and TNF superfamily receptors initiate cascades of intracellular events that ultimately result in destruction of the target cell. Granzyme A targets components of the multi-molecular SET complex, freeing NM23-H1 to cause single stranded DNA nicks. Other Granzyme A substrates include the nuclear Lamins and core and H1 histones. Granzyme B cleaves the pro-apoptotic Bcl-2 family member BID (tBID) and initiates Bax/BAK-mediated release of mitochondrial Cytochrome c. BID cleavage and Cytochrome c release also result from Caspase-8/10 activation following death receptor ligation. Mediators of DNA degradation including AIF and Endo G, and inhibitors of the IAP family, SMAC/Diablo and HtrA2/Omi may also be released from the mitochondria. Cytosolic Cytochrome c binds APAF-1 and Procaspase-9 is recruited/activated, thus forming the apoptosome complex. The effector Procaspases-3 and -7 are potential substrates for Caspase-9, Caspase-8/10, and Granzyme B. Activated effector Caspases and/or Granzyme B target ICAD and release the endonuclease CAD from repression. They may also cleave anti-apoptotic Bcl-2 family member Mcl-1, releasing sequestered pro-apoptotic BIM. Apoptosis cascades are susceptible to regulation by several anti-apoptotic factors including Bcl-2 family members, heat shock proteins (HSP), and several viral proteins. The cellular response to viral infection also includes the secretion of an array of antiviral and immunoregulatory cytokines and chemokines.

Cytotoxic Granule Contents

PROTEIN	FUNCTION
Calreticulin	Binds Perforin and may inhibit Perforin-mediated damage to the effector cell
Cathepsin B	Appears on the cell surface following degranulation and may offer protection from Perforin-mediated self-destruction
Cathepsin C	Processes Granzyme pro-enzymes
Chemokines: RANTES/CCL5, IP-10/CXCL10, and MIP-1α/CCL3	Small proteins capable of mediating chemotaxis and/or cell activation
Fas Ligand/TNFSF6	Potent apoptosis-inducing TNF superfamily member
Granulysin	Human membrane perturbing microbicidal protein that can initiate Cytochrome c release and apoptosis
Granzymes: A, B, C, D, E, F, G, H, K, and M	Serine proteases with roles in Caspase-dependent and -independent apoptosis
H^+ ATPase	Granule acidification
Perforin	Membrane perturbing protein important for Granzyme entry into target cell cytoplasm
Serglycin	Proteoglycan that non-covalently binds Granzymes

Inhibitors of Apoptosis (IAPs)

IAPs	STRUCTURE	TARGET
Apollon/BRUCE		Caspase-3, -9
cIAP-1		Caspase-3, -7, -9
cIAP-2		Caspase-3, -7, -9
ILP-2		Caspase-9
Livin/KIAP/ML-IAP		Caspase-3, -7, -9
NAIP		Caspase-3, -7, -9
Survivin		Caspase-3, -7, -9
XIAP		Caspase-3, -7, -9

DOMAIN KEY

BIR CARD RING UBC

Bcl-2 Family Members

ANTI-APOPTOTIC	STRUCTURE
A1	
Bcl-2	
Bcl-b	
Bcl-w	
Bcl-x_{ES}	
Bcl-x_L	
Boo/DIVA	
Mcl-1	
NR-13	

PRO-APOPTOTIC	STRUCTURE
BAK	
Bax	
Bcl-rambo	
Bcl-x_S	
BOK/Mtd	

BH3-ONLY	STRUCTURE
Bad	
BID	
Bik/Nbk	
BIM	
BLK	
Bmf	
BNIP3	
Hrk/DP5	
Noxa	
PUMA	
Spike	

DOMAIN KEY

BH4 BH3 BH1 BH2 TM

NOTE: This poster conveys a general overview of selected aspects of T cell-mediated cytotoxicity and should not be considered comprehensive nor definitive. The details of the process are understood to be subject to interpretation.

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