## Table of contents

Diphtheria toxin, diphtheria-related fusion protein toxins, and the molecular mechanism of their action against eukaryotic cells ......................... 1
Ryan Ratts and John R. Murphy

Abstract ......................................................................................................... 1
1 Diphtheria toxin .......................................................................................... 1
2 Catalytic domain delivery into the eukaryotic cytosol results in an inhibition of protein synthesis ................................................................. 2
3 Receptor binding and substitution of the native diphtheria toxin receptor binding domain with surrogate ligands ........................................... 3
4 Intoxication of target cells requires the toxin to pass through a low pH endosomal compartment................................................................. 5
5 Internalization of the toxin by receptor mediated endocytosis ............... 6
6 The early endosomal compartment ............................................................ 6
7 The transmembrane domain and channel formation .............................. 8
8 The interchain disulfide bond ................................................................. 9
9 Proposed mechanisms of diphtheria toxin C domain translocation ........ 11
  9.1 Unassisted spontaneous translocation of the diphtheria toxin C domain ................................................................................................. 11
  9.2 A cytosolic translocation factor facilitates the membrane translocation of the diphtheria toxin C domain ............................................. 12
References ................................................................................................... 14

Anthrax toxin and genetic aspects regulating its expression ....................... 21
Amy E. Tucker and Jimmy D. Ballard

Abstract ....................................................................................................... 21
1 Introduction .............................................................................................. 21
2 Overview of anthrax toxin ....................................................................... 22
3 pXO1, the plasmid encoding AT ............................................................. 23
4 The genes of anthrax toxin: pagA, lef, and cya ...................................... 25
5 Environmental signals regulating AT expression ................................... 26
6 AtxA, a global regulator of AT expression ............................................. 27
7 PagR, a negative regulator of PA expression .......................................... 28
8 AbrB, a growth phase-dependent regulator of AT production .............. 29
9 Conclusions and outlook ....................................................................... 30
References ................................................................................................... 31

Shiga toxins and their mechanisms of cell entry ........................................ 35
Kirsten Sandvig, Sébastien Wälchli, and Silje U. Lauvrak

Abstract ....................................................................................................... 35
1 Introduction .............................................................................................. 35
2 Structure of Shiga toxins ....................................................................... 37
3 Toxin interaction with cell surface receptors ........................................... 39
4 Endocytosis of Shiga toxins ...................................................................... 41
5 Endosome to Golgi transport of Shiga toxins ........................................... 42
6 Toxin transport from the trans-Golgi network to the ER ............................. 43
7 Furin-induced cleavage and activation of toxins ........................................ 43
8 Transport from ER to the cytosol............................................................. 44
9 Shiga toxin stimulates secretion of cytokines/chemokines ...................... 44
10 Toxin-induced apoptosis ........................................................................ 45
11 Protection against Shiga toxin-induced disease ...................................... 46
12 Therapeutic use of Shiga toxins ............................................................. 46
13 Conclusions ............................................................................................ 47
Acknowledgements ..................................................................................... 47
References ................................................................................................... 47

Cholera toxin: mechanisms of entry into host cells .......................................... 55
David E. Saslowsky, Michael Kothe, and Wayne I. Lencer ............................ 55
Abstract ....................................................................................................... 55
1 Introduction .............................................................................................. 55
2 Toxin structure ......................................................................................... 56
4 Retrograde transport into the Golgi and ER............................................. 60
   4.1 Possible mechanisms of ganglioside trafficking .............................. 60
   4.2 A direct pathway from TGN to ER ................................................ 61
5 Mechanisms of retro-translocation across the ER membrane ................. 61
6 Conclusions .............................................................................................. 63
Acknowledgements ..................................................................................... 64
References ................................................................................................... 64

ExoU: A cytotoxin delivered by the type III secretion system of
Pseudomonas aeruginosa ........................................................................ 69
Shira D. P. Rabin and Alan R. Hauser ....................................................... 69
Abstract ....................................................................................................... 69
1 Introduction .............................................................................................. 69
2 Discovery ................................................................................................ 70
3 Activity .................................................................................................... 71
   3.1 Cell biological activity .................................................................... 71
   3.2 Enzymatic activity .......................................................................... 72
   3.3 Mechanism of cytotoxicity ............................................................ 75
4 Regulation ............................................................................................... 76
5 ExoU secretion as a variable trait ............................................................ 78
6 Role in virulence ...................................................................................... 81
7 Role in human disease ............................................................................ 82
8 Conclusion ............................................................................................... 83
References ................................................................................................... 83
# Table of contents

## Staphylococcal alpha-toxin

Sucharit Bhakdi, Iwan Walev, Matthias Husmann, and Angela Valeva  
Abstract ................................................. 91  
1 Occurrence and biological significance ........................................ 91  
2 Properties of native toxin .......................................................... 92  
3 Mechanism of action ............................................................... 93  
3.1 Binding ............................................................................... 93  
3.2 Oligomerization ................................................................. 93  
3.3 Pore formation .................................................................... 94  
4 Structure ................................................................................. 95  
4.1 Structure of the heptameric pore formed in detergent solution..... 95  
4.2 Structure of the membrane-bound oligomer ............................ 98  
4.3 Structurally related pore-forming toxins .................................. 98  
5 Cellular resistance and repair mechanisms ................................. 99  
6 Biological effects ........................................................................ 101  
6.1 Cytocidal action .................................................................... 101  
6.2 Secondary cellular reactions ................................................. 101  
6.3 Long-range effects ................................................................ 104  
6.4 Synergism between alpha-toxin and other toxins .................... 104  
7 Use of alpha-toxin in cell biology ............................................. 104  
8 Medical relevance ...................................................................... 105  
Acknowledgements ....................................................................... 106  
References ..................................................................................... 106

## S. cerevisiae K28 toxin - a secreted virus toxin of the A/B family of protein toxins

Susanne Leis, Jenny Spindler, Jochen Reiter, Frank Breinig, and Manfred J. Schmitt  
Abstract ....................................................................................... 111  
1 Introduction ............................................................................... 111  
2 dsRNA viruses cause a killer phenotype in *S. cerevisiae* .............. 112  
2.1 Viral replication cycle ........................................................... 114  
3 Preprotoxin processing and toxin secretion ................................ 115  
4 Toxin uptake and retrograde transport ....................................... 116  
4.1 A single disulfide bond between α and β exposes the ER targeting signal of the toxin ................................................. 119  
4.2 Toxin dislocation out of the ER .............................................. 120  
5 Mode of K28 toxin action ......................................................... 122  
5.1 Toxin-induced apoptotic host cell responses ............................ 124  
6 Toxin immunity .......................................................................... 125  
7 Concluding remarks ................................................................... 126  
Acknowledgements ....................................................................... 126  
References ..................................................................................... 127
# Table of contents

**Kluyveromyces lactis** zymocin and other plasmid-encoded yeast killer toxins ........................................... 133

Raffael Schaffrath and Friedhelm Meinhardt ................................................................. 133

Abstract ......................................................................................................................... 133

1 Introduction .................................................................................................................. 133

2 The plasmid-encoded killer system from *Kluyveromyces lactis* .................. 134

   2.1 Plasmid structures, genome organizations, and gene functions .......... 134

   2.2 Molecular genetic manipulation, gene shuffles, and applications .. 135

3 The *K. lactis* zymocin complex .............................................................................. 136

   3.1 Zymocin subunit composition and biogenesis ............................................. 136

   3.2 Functional assignment of individual zymocin subunits ....................... 137

   3.3 Autoimmunity of *K. lactis* zymocin producers ...................................... 137

4 The zymocin response pathway of *S. cerevisiae* ........................................ 138

   4.1 Target yeast spectrum and anti-proliferative effects ....................... 138

   4.2 Zymocin sensitivity conferring genes and zymocin resistance ......... 138

   4.3 Zymocin docking and early response events ...................................... 139

   4.4 Toxin-target capacity of the RNA polymerase II Elongator complex ........................................... 141

   4.5 Other factors linked to Elongator’s TOT function .............................. 142

   4.6 Zymocin mode of action: a working model ........................................ 144

5 Zymocin-related yeast killer systems ................................................................. 145

6 Conclusions ............................................................................................................... 146

Acknowledgements ........................................................................................................ 147

References ...................................................................................................................... 148

**The Ustilago maydis** killer toxins ........................................................................ 157

Jeremy Bruenn .............................................................................................................. 157

Abstract ......................................................................................................................... 157

1 Introduction .................................................................................................................. 157

2 KP1 toxin ................................................................................................................... 159

   2.1 Synthesis ................................................................................................. 159

   2.2 Structure, mechanism of action, and heterologous expression ...... 159

3 KP4 toxin ................................................................................................................... 160

   3.1 Synthesis ................................................................................................. 160

   3.2 Structure ................................................................................................. 160

   3.3 Mechanism of action .............................................................................. 162

   3.4 Heterologous expression ...................................................................... 164

4 KP6 toxin ................................................................................................................... 165

   4.1 Synthesis ................................................................................................. 165

   4.2 Structure ................................................................................................. 166

   4.3 Mechanism of action .............................................................................. 167

   4.4 Heterologous expression ...................................................................... 168

5 Summary ..................................................................................................................... 168

References ...................................................................................................................... 169
Zygocin – a monomeric protein toxin secreted by virus-infected Zygosaccharomyces bailii

Frank Weiler and Manfred J. Schmitt

Abstract

1 Zygocin is genetically encoded by a dsRNA “killer” virus
2 Zygocin is synthesized as an inactive precursor
3 Zygocin toxicity involves disruption of cellular integrity
4 Identification of host genes conferring zygocin resistance
5 Zygocin as novel antimycotic

Acknowledgements

References

Acidophilic structure and killing mechanism of the Pichia farinosa killer toxin SMKT

Chise Suzuki

Abstract

1 Introduction
2 Properties of a halotolerant killer yeast, Pichia farinosa
3 SMKT with an acidophilic subunit structure
   3.1 SMKT consists of two distinct subunits
   3.2 SMKT preprotoxin encoded by the chromosomal gene and the maturation process
   3.3 Lethal effect of expression of SMK1 in S. cerevisiae
   3.4 Crystal structure of SMKT
   3.5 Stable state and dissociation process of SMKT
4 P-type ATPase SPF1 required for sensitivity to SMKT
   4.1 SPF1 encoding a novel P-type ATPase
   4.2 Feature of type V P-type ATPases
   4.3 Localization of Spf1p
   4.4 Phenotypes of disruptants of SPF1
   4.5 Comparison of intracellular roles of Spf1p and Pmr1p
5 Killing and resistant mechanism of SMKT
   5.1 SMKT interacts with the cell surface of resistant cells
   5.2 Interaction of SMKT with cell membranes
6 Concluding remarks

Acknowledgements

References
**Ricin: structure, synthesis, and mode of action**

J. Michael Lord and Lynne M. Roberts

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abstract</td>
<td>215</td>
</tr>
<tr>
<td>Discovery</td>
<td>215</td>
</tr>
<tr>
<td>Ricin structure</td>
<td>216</td>
</tr>
<tr>
<td>Function of the ricin subunits</td>
<td>217</td>
</tr>
<tr>
<td>Ricin biosynthesis</td>
<td>218</td>
</tr>
<tr>
<td>Ricin intoxication of mammalian cells</td>
<td>221</td>
</tr>
<tr>
<td>Endocytosis to the Golgi</td>
<td>221</td>
</tr>
<tr>
<td>Golgi to ER transport</td>
<td>222</td>
</tr>
<tr>
<td>Membrane translocation of ricin</td>
<td>224</td>
</tr>
<tr>
<td>Concluding comments</td>
<td>226</td>
</tr>
<tr>
<td>References</td>
<td>227</td>
</tr>
</tbody>
</table>
Microbial Protein Toxins
Schmitt, M.J.; Schaffrath, R. (Eds.)
2005, XIV, 237 p. 41 illus., 6 illus. in color., Hardcover
ISBN: 978-3-540-23562-0