Uptake and function of anthrax toxins

D'Eustachio, P., Jassal, B., Leppla, SH., Liu, S., Moayeri, M., Shoichet, BK., Turk, BE.

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01/05/2021
Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references


Reactome database release: 76

This document contains 1 pathway and 20 reactions (see Table of Contents)
Bacillus anthracis bacteria target cells in an infected human through the action of three secreted bacterial proteins, lef (also known as LF, lethal factor), cya (also known as EF, edema factor), and pagA (also known as PA, protective antigen) (Turk 2007; Young and Collier 2007). lef is a protease that cleaves and inactivates many MAP2K (MAP kinase kinase, MEK) proteins (Duesbery et al. 1998; Vitale et al. 2000), disrupting MAP kinase signaling pathways. cya is an adenylate cyclase that mediates the constitutive production of cAMP (Leppla 1982), a molecule normally generated transiently in tightly regulated amounts in response to extracellular signals. Both lef and cya depend on pagA to enter their target cells, a strategy characteristic of bacterial binary toxins (Barth et al. 2004). pagA binds to the target cell receptors, is cleaved by furin or other cellular proteases, and thereafter forms an oligomer that exposes binding sites for lef and cya molecules (Young and Collier 2007). This complex is taken into the target cell by clathrin mediated endocytosis and delivered to endosomes. The low pH of the endosome causes the bacterial toxin complex to rearrange: the pagA oligomer forms a pore in the endosome membrane through which lef and cya molecules enter the target cell cytosol.

**Literature references**


### Editions

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pagA binds ANTXR1

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5210921

Type: binding

Compartments: extracellular region, plasma membrane

Diseases: anthrax disease

Extracellular pagA (also known as PA83 - full length Protective Antigen - Petosa et al. 1997) produced by Bacillus anthracis binds to either of two isoforms of ANTXR1 (Anthrax Toxin Receptor 1, also known as TEM8 - Bradley et al. 2001; Liu and Leppla 2003) in the plasma membrane of a target human cell. The physiological ligand for ANTXR1 is not known nor are the physiological roles of the two ANTRX1 isoforms. Although ANTXR1 can act as a relatively low affinity pagA receptor in tissue culture model systems, it does not play a primary role in anthrax toxin induced effects in mouse models (Liu et al. 2009). While some studies suggest that ANTXR1 is associated with palmitoylated LRP6 (low density lipoprotein receptor related protein 6 - Abrami et al. 2008) in the plasma membrane and that the latter molecule can function as a co-receptor (Wei et al. 2006), the role of LRP6 in PA83 uptake remains uncertain (reviewed by van der Goot & Young 2009) and no function for LRP6 is annotated here.

Followed by: Furin cleaves ANTXR1-bound pagA to yield pagA(197-794)

Literature references


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pagA binds ANTXR2

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5210918

Type: binding

Compartments: extracellular region, plasma membrane

Diseases: anthrax disease

Extracellular pagA (PA83, full length Protective Antigen - Petosa et al. 1997) produced by Bacillus anthracis binds to either of two isoforms of ANTXR2 (Anthrax Toxin Receptor 2, also known as CMG2 - Scobie et al. 2003) in the plasma membrane of a target human cell. The physiological ligand for ANTXR2 is not known, but this receptor has been shown to be the primary receptor involved in anthrax toxin pathogenesis (Liu et al. 2009). While some studies suggest that ANTXR2 is associated with palmitoylated LRP6 (low density lipoprotein receptor related protein 6 - Abrami et al. 2008) in the plasma membrane and that the latter protein can function as a co-receptor (Wei et al. 2006), the role of LRP6 in PA83 uptake remains uncertain (reviewed by van der Goot & Young 2009) and no function for LRP6 is annotated here.

Followed by: Furin cleaves ANTXR2-bound pagA to yield pagA(197-794)

Literature references


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Furin cleaves ANTXR1-bound pagA to yield pagA(197-794)

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5210935

Type: transition

Compartments: extracellular region, plasma membrane

Diseases: anthrax disease

Furin or a related protease at the cell surface cleaves ANTXR1-bound pagA (Anthrax Protective Antigen, full-length). The larger cleavage product, pagA(197-794), remains bound to the receptor while a smaller product, pagA(30-196), is released into the extracellular space (Klimpel et al, 1992; Molloy et al. 1992).

Preceded by: pagA binds ANTXR1

Followed by: ANTXR1-bound pagA(197-794) forms oligomers

Literature references


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Furin cleaves ANTXR2-bound pagA to yield pagA(197-794)

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5210912

**Type:** transition

**Compartments:** extracellular region, plasma membrane

**Diseases:** anthrax disease

Furin or a related protease at the cell surface cleaves ANTXR2-bound pagA (Anthrax Protective Antigen, full-length). The larger cleavage product, pagA(197-794), remains bound to the receptor while a smaller product, pagA(30-196), is released into the extracellular space (Klimpel et al, 1992; Molloy et al. 1992).

**Preceded by:** pagA binds ANTXR2

**Followed by:** ANTXR2-bound pagA(197-794) forms oligomers

**Literature references**


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FURIN binds furin inhibitors

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-9683546

**Type:** binding

**Compartments:** extracellular region, plasma membrane

Furin and related proprotein convertases (PCs) cleave the multibasic motifs R-X-R/K/X-R in precursor proteins, transforming latent proproteins into biologically active proteins and peptides. Furin is present both in the intracellular secretory pathway and at the cell surface. Intracellular furin processes its multiple normal cellular targets in the Golgi and secretory vesicle compartments. Cell surface furin-mediated cleavage of coat proteins of viral pathogens including influenza A-H5N1 (bird flu), flaviviruses, and Marburg and Ebola viruses and of anthrax and botulinum toxins, enables entry into host cells to cause disease onset (Braun & Sauter 2019). Cell surface furin inhibitors capric acid, pirfenidone (Burghardt et al. 2007) and MI-1148 (Hardes et al. 2015) inhibit furin activity thereby exhibiting a protective effect against some toxins and inhibiting the spread of several pathogenic viruses (Hardes et al. 2015). Inhibitors of PCs represent a potential therapeutic anti-SARS activity (Bergeron et al. 2005, Izaguirre 2019).

**Literature references**


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ANTXR1-bound pagA(197-794) forms oligomers

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5210909

**Type:** binding

**Compartments:** plasma membrane

**Diseases:** anthrax disease

ANTXR1 (Anthrax Receptor 1)-bound pagA(197-794) (protective antigen, large fragment) forms oligomers in the target cell plasma membrane. Initial studies indicated that these were heptamers (Lacy et al. 2004; Santelli et al. 2004; Wigelsworth et al. 2004; Young and Collier 2007). More recent work has established that octamers also form and suggests that the octaneric structure is more stable under physiological conditions (Kintzer et al. 2009, 2010). Formation of the latter structure is thus annotated here.

**Preceded by:** Furin cleaves ANTXR1-bound pagA to yield pagA(197-794)

**Followed by:** cya and lef bind to pagA(197-794):ANTXR1 oligomer

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ANTXR2-bound pagA(197-794) forms oligomers

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5210932

**Type:** binding

**Compartments:** plasma membrane

**Diseases:** anthrax disease

ANTXR2 (Anthrax Receptor 2)-bound pagA(197-794) (protective antigen, large fragment) forms oligomers in the target cell plasma membrane. Initial studies indicated that these were heptamers (Lacy et al. 2004; Santelli et al. 2004; Wigelsworth et al. 2004; Young and Collier 2007). More recent work has established that octamers also form and suggests that the octaneric structure is more stable under physiological conditions (Kintzer et al. 2009, 2010). Formation of the latter structure is thus annotated here.

**Preceded by:** Furin cleaves ANTXR2-bound pagA to yield pagA(197-794)

**Followed by:** cya and lef bind to pagA(197-794):ANTXR2 oligomer

**Literature references**


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The enzyme components of anthrax toxins cya (also known as EF, Edema Factor - Robertson et al. 1988) and lef (also known as LF, Lethal Factor - Bragg & Robertson 1989; Klimpel et al. 1994) bind to pagA(197-794):ANTXR1 (protective antigen, large fragment: Anthrax receptor 1) oligomers on the target cell surface. Binding of the two toxins to an oligomer is competitive and as many as four toxin molecules can bind to one oligomer (Elliott et al. 2000; Pimental et al. 2004).

**Preceded by:** ANTXR1-bound pagA(197-794) forms oligomers

**Followed by:** Endocytosis of cya:lef:(pagA(197-794):ANTXR1 oligomer) (plasma membrane to endosome membrane)

**Literature references**


cyA and lef bind to pagA(197-794):ANTXR2 oligomer

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5210892

**Type:** binding

**Compartments:** extracellular region, plasma membrane

**Diseases:** anthrax disease

The enzyme components of anthrax toxins cya (also known as EF, Edema Factor - Robertson et al. 1988) and lef (also known as LF, Lethal Factor - Bragg & Robertson 1989; Klimpel et al. 1994) bind to pagA(197-794):ANTXR2 (protective antigen, large fragment: Anthrax receptor 2) oligomers on the target cell surface. Binding of the two toxins to an oligomer is competitive and as many as four toxin molecules can bind to one oligomer (Elliott et al. 2000; Pimental et al. 2004).

**Preceded by:** ANTXR2-bound pagA(197-794) forms oligomers

**Followed by:** Endocytosis of cya:lef:(pagA(197-794):ANTXR2 oligomer) (plasma membrane to endosome membrane)

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Endocytosis of cya:lef:(pagA(197-794):ANTXR1 oligomer) (plasma membrane to endosome membrane)

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5210944

Type: omitted

Compartments: plasma membrane, endosome membrane

Diseases: anthrax disease

cya (Anthrax EF, edema factor) and lef (LF, lethal factor) toxins bound to pagA(197-794):ANTXR1 (protective antigen, large fragment:Anthrax receptor 1) oligomer on the plasma membrane of the target cell, are localized into clathrin coated vesicles and transported to endosomes. Depletion of target cell ARAP3 (ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3) partly blocks endocytosis (Lu et al. 2004), but this effect may be indirect and has not been characterized at a molecular level (van der Goot & Young 2009).

Preceded by: cya and lef bind to pagA(197-794):ANTXR1 oligomer

Followed by: pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol)

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Endocytosis of cya:lef:(pagA(197-794):ANTXR2 oligomer) (plasma membrane to endosome membrane)

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5210959

Type: omitted

Compartments: plasma membrane, endosome membrane

Diseases: anthrax disease

cya (Anthrax EF, edema factor) and lef (LF, lethal factor) toxins bound to pagA(197-794):ANTXR2 (protective antigen, large fragment:Anthrax receptor 1) oligomer on the plasma membrane of the target cell, are localized into clathrin coated vesicles and transported to endosomes. Depletion of target cell ARAP3 (ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 3) partly blocks endocytosis (Lu et al. 2004), but this effect may be indirect and has not been characterized at a molecular level (van der Goot & Young 2009).

Preceded by: cya and lef bind to pagA(197-794):ANTXR2 oligomer

Followed by: pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol)

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5210947

**Type:** omitted

**Compartments:** endosome membrane, cytosol

**Diseases:** anthrax disease

Through the action of vacuolar ATPase the pH of the target cell early endosome is lowered. In this environment, pagA (197-794) (PA63, Anthrax protective antigen, large fragment) dissociates from its receptor and forms an oligomeric channel in the endosome membrane through which the anthrax cya (EF, edema factor) and lef (LF, lethal factor) pass (Milne et al. 1994). Entry of cya and lef into the target cell cytosol is thought to be mediated by back fusion of intraluminal vesicles with the late endosomal membrane and to be positively regulated by PDCD6IP / ALIX protein (Abrami et al. 2004).

**Preceded by:** Endocytosis of cya:lef:(pagA(197-794):ANTXR1 oligomer) (plasma membrane to endosome membrane)

**Followed by:** Anthrax cya catalyzes the conversion of ATP to cAMP, Anthrax lef cleaves target cell MAP2K7 (MEK7), Anthrax lef cleaves target cell MAP2K2 (MEK2), Anthrax lef cleaves target cell MAP2K4 (MEK4), Anthrax lef cleaves target cell MAP2K3 (MEK3), Anthrax lef cleaves target cell MAP2K1 (MEK1), Anthrax lef cleaves target cell MAP2K6 (MEK6)

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pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5210943

**Type:** omitted

**Compartments:** endosome membrane, cytosol

**Diseases:** anthrax disease

Through the action of vacuolar ATPase the pH of the target cell early endosome is lowered. In this environment, pagA (PA63, Anthrax protective antigen, large fragment) dissociates from its receptor and forms an oligomeric channel in the endosome membrane through which the anthrax cya (EF, edema factor) and lef (LF, lethal factor) pass (Milne et al. 1994). Entry of cya and lef into the target cell cytosol is thought to be mediated by back fusion of intraluminal vesicles with the late endosomal membrane and to be positively regulated by PDCD6IP / ALIX protein (Abrami et al. 2004).

**Preceded by:** Endocytosis of cya:lef:(pagA(197-794):ANTXR2 oligomer) (plasma membrane to endosome membrane)

**Followed by:** Anthrax cya catalyzes the conversion of ATP to cAMP, Anthrax lef cleaves target cell MAP2K7 (MEK7), Anthrax lef cleaves target cell MAP2K2 (MEK2), Anthrax lef cleaves target cell MAP2K4 (MEK4), Anthrax lef cleaves target cell MAP2K3 (MEK3), Anthrax lef cleaves target cell MAP2K1 (MEK1), Anthrax lef cleaves target cell MAP2K6 (MEK6)

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Anthrax cya catalyzes the conversion of ATP to cAMP

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5211224

**Type:** transition

**Compartments:** cytosol

**Diseases:** anthrax disease

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cya (EF, edema factor), transported to the cytosol of the target cell, catalyzes the synthesis of cAMP from ATP, in a reaction that requires target cell calmodulin (Leppla 1984; Labruyere et al. 1990).

**Preceded by:** pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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Anthrax lef cleaves target cell MAP2K1 (MEK1)

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5211340

Type: transition

Compartments: cytosol

Diseases: anthrax disease

lef (Anthrax LF, lethal factor), a zinc metalloprotease (Klimpel et al, 1994) in the target cell cytosol, cleaves MAP2K1 (MEK1, mitogen activated protein kinase kinase 1) at the N-terminus. While the kinase domain of MAP2K1 is unaffected, an aminoterminal docking domain is disrupted by the cleavage and the protein fails to interact normally with substrates (Duesbery et al. 1998; Vitale et al. 1998).

Preceded by: pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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Anthrax lef cleaves target cell MAP2K2 (MEK2)

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5211356

**Type:** transition

**Compartments:** cytosol

**Diseases:** anthrax disease

lef (Anthrax LF, lethal factor) a zinc metalloprotease (Klimpel et al, 1994) in the target cell cytosol, cleaves MAP2K2 (MEK2, mitogen activated protein kinase kinase 2). While the kinase domain of MAP2K2 is unaffected, an aminoterminal docking domain is disrupted by the cleavage (Duesbery et al. 1998; Vitale et al. 1998).

**Preceded by:** pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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Anthrax lef cleaves target cell MAP2K3 (MEK3)

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5211400

**Type:** transition

**Compartments:** cytosol

**Diseases:** anthrax disease

lef (Anthrax LF, lethal factor) a zinc metalloprotease (Klimpel et al, 1994) in the target cell cytosol, cleaves MAP2K3 (MEK3, mitogen activated protein kinase kinase 3), isoform 3 (Pellizzari et al. 1999).

**Preceded by:** pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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Anthrax lef cleaves target cell MAP2K4 (MEK4)

**Location:** Uptake and function of anthrax toxins

**Stable identifier:** R-HSA-5211391

**Type:** transition

**Compartments:** cytosol

**Diseases:** anthrax disease

lef (Anthrax LF, lethal factor) a zinc metalloprotease (Klimpel et al, 1994) in the target cell cytosol, cleaves MAP2K4 (MEK4, mitogen activated protein kinase kinase 4) (Vitale et al. 2000).

**Preceded by:** pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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https://reactome.org
**Anthrax lef cleaves target cell MAP2K6 (MEK6)**

**Location:** Uptake and function of anthrax toxins  
**Stable identifier:** R-HSA-5211405  
**Type:** transition  
**Compartments:** cytosol  
**Diseases:** anthrax disease

lef (Anthrax LF, lethal factor) a zinc metalloprotease (Klimpel et al, 1994) in the target cell cytosol, cleaves MAP2K6 (MEK6, mitogen activated protein kinase kinase 6), isoform 1 (Vitale et al. 2000).

**Preceded by:** pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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Anthrax lef cleaves target cell MAP2K7 (MEK7)

Location: Uptake and function of anthrax toxins

Stable identifier: R-HSA-5211387

Type: transition

Compartments: cytosol

Diseases: anthrax disease

lef (Anthrax LF, lethal factor) a zinc metalloprotease (Klimpel et al, 1994) in the target cell cytosol, cleaves MAP2K7 (MEK7, mitogen activated protein kinase kinase 7) (Vitale et al. 2000).

Preceded by: pagA(197-794):ANTRX1 oligomer transports cya and lef (target cell endosome to cytosol), pagA(197-794):ANTRX2 oligomer transports cya and lef (target cell endosome to cytosol)

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