genomics with care

MINDING THE DOUBLE BINDS OF SCIENCE • MIKE FORTUN

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EXPERIMENTAL FUTURES:
TECHNOLOGICAL LIVES,
SCIENTIFIC ARTS,
ANTHROPOLOGICAL VOICES
A series edited by Michael M. J. Fischer and Joseph Dumit

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POEM-LIKE *TOLLS* 1 ·

a prelude

Establishment of Dorsal-Ventral Polarity in
the *Drosophila* Embryo: Genetic Studies on the
Role of the *Toll* Gene Product KATHRYN V. ANDERSON,
GERD JÜRGENS, AND CHRISTIANE NÜSSLEIN-VOLHARD

In the course of a number
of mutant screens
in which isogenic lines were established

six totally penetrant
dominant maternal effect
mutations were identified and recovered
(see Experimental Procedures).

Females heterozygous
for each of the mutations
produce embryos that develop and differentiate
cuticles of characteristically
mutant pattern.

Four of these
dominant maternal effect
mutations share a common embryonic phenotype,
the *Toll* phenotype. The
cuticle pattern
of *Toll*^{D} embryos differs strikingly from the
wild-type pattern.

Instead of the characteristic array of
denticle bands ventrally
and fine hairs dorsally,
Toll^{D} embryos have rings or patches of
ventricle denticles
along the entire dorsal-ventral circumference and
lack dorsal hairs altogether.
Other structures normally
derived from dorsal and dorsolateral
anlagen are also missing:
filzkörper, spiracles,
head sensory organs
and the head skeleton are
all absent.

Early
in the development of *Toll*^{D} embryos,
the pattern
of morphogenetic movements
at gastrulation also
shows a loss of dorsal,
and expansion of ventral,
pattern elements.

Several observations suggest
that there is a direct interaction
between the copies of the *Toll* gene product.
Two of the four dominant
alleles, *Tl*^{sB} and *Tl*^{B4C},
behave like amorphic alleles when placed in
trans to a deficiency.

The products of these alleles are thus inactive
on their own, yet
in combination with the wild-type product produce
an abnormal activity.

Two classes
of models could explain
the specific interactions seen between
Toll alleles. One model is that the
Toll protein product is present
as a dimer or multimer
whose activity depends on interactions between subunits.
An alternative
model is that the active *Toll* product
autocatalytically promotes the further
activation of other copies
of the *Toll* product.

The autocatalytic mechanism is attractive . . .

However, the data
currently available
do not allow
us to distinguish
between these two classes of models.

The system that establishes
dorsal-ventral positional information
in the embryo requires the action
of nine maternal effect dorsal-group genes in addition
to *Toll*.

In the absence of
any one of these components, all cells differentiate
according to a dorsal ground state.
The simple model
in which each of these genes controls
one step in a linear biochemical
pathway leading to the production of a ventralizing

morphogen is ruled out
by the double mutations of the recessive alleles of
other dorsal-group genes with Tl^{9Q}
since in the presence of Tl^{9Q}
ventrolaterally derived structures can be produced
in the absence of
gastrulation-defective, nudel*, pipe*, snake*, or *easter**.

The working model we find
most attractive
is diagrammed in Figure 6 . . .
Both the active form
of the *Toll* product and the products
of the other dorsalizing genes
(*gd*, ndl*, pip*, snk*, ea**)
are required
in a way that we do not yet understand . . .

A Family of Human Receptors Structurally Related to *Drosophila Toll*

FERNANDO L. ROCK, GARY HARDIMAN, JACKIE C. TIMANS, ROBERT A. KASTELEIN, AND J. FERNANDO BAZAN

The seeds of the
morphogenetic gulf
that so dramatically separates
flies from humans
are planted
in familiar embryonic
shapes and patterns
but
give rise to very different
cell complexities.

This divergence
of developmental plans between
insects and vertebrates

is choreographed
by remarkably similar signaling pathways,
underscoring
a greater conservation of protein networks and
biochemical mechanisms from unequal
gene repertoires.

A universally critical
step in embryonic development is the
specification of body axes, either born
from innate asymmetries or triggered
by external cues.

We describe the cloning
and molecular characterization of five
Toll-like molecules in humans
—named TLRs 1–5—
that reveal a receptor family more
closely tied
to *Drosophila Toll* homologs than to vertebrate
IL-1Rs. Spurred
by other efforts, we are assembling,
by structural conservation and molecular parsimony,
a biological system in humans that is
the counterpart of a compelling
regulatory scheme
in *Drosophila*

This signaling pathway centers on *Toll*, a
transmembrane receptor that transduces
the binding of a maternally secreted ventral
factor, Spätzle,
into the cytoplasmic engagement of
Tube, an accessory
molecule, and the activation of
Pelle, a Ser/Thr
kinase that catalyzes the
dissociation of Dorsal
from the inhibitor

Cactus and
allows migration of
Dorsal to ventral
nuclei.

The *Toll*
pathway also controls
the induction of potent antimicrobial
factors in the adult fly; this role
in *Drosophila* immune
defense strengthens mechanistic parallels
to interleukin pathways
that govern a host of immune and
inflammatory responses in
vertebrates.

A *Toll*-
related cytoplasmic domain directs the
binding of a Pelle-like
kinase, IRAK, and the
activation of a latent
NF-kByI-kB complex that
mirrors the embrace
of Dorsal and Cactus.

Components of an Evolutionarily Ancient Regulatory System.

The evolutionary link
between insect and vertebrate immune systems is
stamped in DNA:
genes encoding antimicrobial factors in insects
display upstream motifs
similar to acute-phase response
elements known to bind NF-kB transcription factors in mammals.

Dorsal and two Dorsal-
related factors,
Dif and Relish,
help induce these defense proteins after

bacterial challenge; *Toll* or other TLRs probably
modulate these rapid immune responses
in adult *Drosophila*.
These mechanistic parallels
to the IL-1 inflammatory response in vertebrates
are evidence
of the functional versatility
of the *Toll* signaling pathway
and suggest an ancient synergy
between embryonic patterning
and innate immunity

perhaps the distinct
cellular contexts
of compact embryos and
gangly adults simply result
in familiar signaling pathways and their
diffusible triggers having
different biological outcomes at
different times

Human TLRs and IL-1Rs in Host Defense: Natural Insights from Evolutionary, Epidemiological, and Clinical Genetics

JEAN-LAURENT CASANOVA, LAURENT ABEL, AND LLUIS QUINTANA-MURCI

The immunological saga
of *Toll*-like receptors (TLRs) began with the
seminal discovery
in 1981 that antimicrobial peptides are a key
mechanism of innate host defense
in insects.

This was followed by
the observation in 1991 that the fruit fly
Drosophila melanogaster Toll

and mammalian interleukin-1 receptor
have an intracellular domain
in common. These studies
paved the way for elucidation of
the role of *Toll* in controlling
the synthesis of some
of these peptides in *Drosophila*.

These discoveries soon led
to the identification of a human
TLR, followed by
the discovery of a function for
TLRs with the demonstration that
lipopolysaccharide (LPS) responses were
abolished
in mice with spontaneous TLR4 mutations.

The similarities
between the *Toll* and TLR
signaling pathways
in invertebrates and vertebrates
were initially interpreted
as evidence of a common
ancestry for these defense mechanisms and
subsequently of convergent evolution,
emphasizing their evolutionary
importance.

The 15 years or so following
these findings have witnessed a substantial
rise in interest in
the role of *Toll*
in *Drosophila* immunity,
of TLRs in mouse host defense,
and even of TLRs in diverse other animal species.

Indeed, interest
in TLRs has been such that just about
any immunological phenomenon imaginable—

ranging from host defense and tumor immunity
to allergy and autoimmunity—has been examined from
a TLR perspective.

This phenomenon
has even extended to processes only
remotely connected with immunity,
such as atherosclerosis and
degenerative diseases, and
has also stimulated research into the role of human
TLRs in the pathogenesis of most,
if not all,
human diseases.

Various schools of immunological
thought have conferred different names
on pathogen receptors, including
pathogen associated molecular pattern (PAMP) recognition receptors,
pattern-recognition receptors (PRRs),
innate immune sensors,
and microbial sensors.
Whatever the terminology
used, the underlying
idea is that TLRs detect
a wide range of microorganisms,
discriminating between these microbes and
distinguishing them from self on the basis of
their type, through the detection of
specific, conserved
microbial patterns, molecular patterns, or molecules.

Does this commonly expressed view of
TLRs and IL-IRs reflect the biological
reality?
Like most immunological
knowledge, it is based mostly on experiments conducted in
the mouse model.
However rigorous, accurate, and thorough
such experiments are, can experimental

findings in mice really provide a
faithful and reliable representation of host defense
and protective immunity in other species,
in their natural setting?

There are differences between species, including several
identified differences between humans and mice, and
immunological generalizations from
a single species may be
perilous.