Role of Activin, Inhibin, Folistatin and Alramin Proteins in Inflammation

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- Activins are members of the TGFβ superfamily
- In addition to its role in modulating FSH release from the pituitary, activin A is involved in
  - **erythroid** differentiation,
  - **mesoderm** induction,
  - **neuron survival**
  - **plasmacytoma cell inhibition**
- others are activin B and activin AB
- The inhibins are members of the same TGF β subfamily to which the activins belong
- Inhibins are largely regarded as endocrine factors to **modulate FSH release** from the pituitary.
- Inhibins also act as **negative regulators of activin** activity

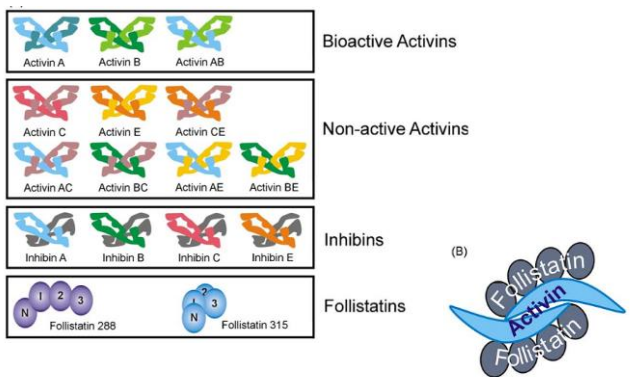

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Table 1
Clinical inflammatory syndromes in which activins and follistatin have been implicated.

Clinical pathology	Involvement of activins and follistatin
Septicemia	Both activin A and follistatin elevated in circulation; activin levels indicate patient outcome
Food poisoning	Follistatin elevated in circulation some days after ingestion
Acute coronary syndromes	Circulating activin elevated in stable and unstable angina; elevated in heart failure
Inflammatory bowel disease	Increased expression of β_A subunit mRNA in gut of Crohn's and ulcerative colitis patients
Meningitis	Increased activin A and follistatin concentrations in cerebrospinal fluid
Traumatic brain injury (TBI)	Cerebrospinal fluid concentrations elevated in some patients following isolated TBI
Burn injury	Increased localisation in infiltrating immune cells invading the burn injury site
Asthma	Higher serum activin A and elevated β_A and β_B subunit mRNA levels in white blood cells
Atopic dermatitis	Increased β_A and β_B subunit mRNAs in peripheral blood cells
Rheumatoid arthritis	Increased localisation in synovial tissues and elevated synovial fluid concentrations
Pre-eclampsia	Elevated maternal serum concentrations of activin A in pre-eclamptic pregnancies

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- **Activins** signal through a Type I/Type II receptor complex and utilize **Smads**, conserved proteins that **shuttle** between the membrane-bound receptors and the nucleus, to initiate intracellular signal transduction
- **Activin A** is released within **40 min of LPS** administration in sheep, slightly earlier than **TNFa** and well before any elevation in IL-6

- The **second phase** of activin A release is few hours after acute inflammatory activation through classical inflammatory pathways.
- Activin A in acute inflammation is **pre-stored release** from responsive cells, whereas the latter release is largely composed of newly synthesized material
- Activin A can be synthesized by almost **every cell type** in the body
  - A number of cell types are known to **produce** activin under inflammatory stimuli, such as **monocytes**, **macrophages**, **dendritic cells** and **endothelial cells**
- Activin A is released after PAMPs (**LPS**) trigger activation of TLR pathways, especially **TLR4**, through **MyD88** adaptor protein

- **TREM-1** represents an alternative pathway distinct from TLRs in response to detection of PAMPs, and confirms a central position of activin release in innate immunity
- activin has both **pro-inflammatory** and **regulatory activities**: promoting inflammatory responses in the absence of a pre-existing inflammation or activation state, but inhibiting on-going or established inflammatory and immune processes

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- activin A inhibits thymocyte and peripheral T cell activation
- **inhibits plasmacytoma** growth and survival
- apparently plays another important role by stimulating the activation and **IgG production** response to LPS
- promote human monocyte differentiation to **dendritic cells**
- activin A inhibits **macrophage foam cell** formation
- follistatin promotes **macrophage foam cell** formation
- Activin A is mainly involved in **acute inflammation** but the involvement in chronic conditions has also been described (Crohn's Disease, rheumatoid arthritis and gout, etc.)

- **Follistatin** has the capacity to bind and neutralise the actions of other members of the TGFβ superfamily
- **Follistatin** increase in blood has been noticed after surgical **castration** in **sheep** after 7-19 hours of surgery
- **follistatin** can block all the biological effects of the activins
- By blocking the effects of activin, the mortality can be markedly reduced
- The 'therapeutic' use of follistatin in inflammatory pathologies has enormous potential in the clinical setting.

Alarmins

- **Neutrophils** are the first major population of leukocyte to infiltrate infected or injured tissues and are crucial for initiating host innate defense and adaptive immunity
- The role in innate immune defense is mediated predominantly by phagocytosis and killing of microorganisms
- neutrophils also participate in the induction of adaptive immune responses
- At sites of infection and/or injury, neutrophils release numerous mediators upon degranulation or death, among these are alarmins which mobilize and activate **antigen presenting cells**

- Neutrophils are rapidly induced to degranulate in the inflammatory microenvironment by a wide variety of stimulants such as formyl-methionyl-leucyl-phenylalanine (fMLF), C5a, PAF, LPS and TNF
- The term alarmins are used because they represent the **first host response** to exogenous (infections) and endogenous (injuries) danger signals
- Alarmins help to **produce cytokines** by inflammatory cells and to cause maturation of DCs capable of inducing antigen-specific adaptive immune responses

- Alarmins are present in cells, such as **leukocytes** and **epithelial cell**s as components of the granules
- are **rapidly released** by degranulation and/or cell necrosis in response to infection or tissue injury
- Alarmins are endogenous peptides that are released in host defense against danger signals (**DAMP**).
- recruit leukocytes from the **blood** and activate many nearby cells
- The **recruitment and activation** of neutrophils, monocytes/macrophages, dendritic cells and NK cells by alarmins enhances the inflammatory response
- The activity occur through TLRs

- **Neutrophil-derived alarmins** include a number of human antimicrobial peptides such as
  - α-defensins
  - Cathelicidin
  - Lactoferrin
  - In addition, cell injury/necrosis of neutrophils results in the release of nuclear binding proteins with alarmin activity, such as **high-mobility group box-1** (HMGB1) protein

α-defensins

- are small (3–4 kDa) cationic host-derived antimicrobial peptides isolated from the azurophilic granules
- They are particularly abundant in
  - **neutrophils**,
  - certain **macrophages** and
  - **Paneth cells** of the small intestine
    - are active at micromolar concentrations
    - against many **bacteria**, **fungi** and **enveloped viruses**.
- Initially characterized as antimicrobial agent, but also have immuno-stimulatory properties
- **chemo-attract** a variety of leukocytes to inflammatory sites

- Also induce the expression of cytokines and chemokines including IL-1, TNF, IL-8 and **monocyte chemo-attractant protein-1** (MCP-1)

Cathelicidins

- Are mammalian antimicrobial proteins
- More than 40 members of the cathelicidin family have been identified in different species
- however, humans and mice each produce only one cathelicidin, called **human cationic antimicrobial protein 18** (hCAP18)
- Cathelicidins are predominantly stored in the secondary granules of **neutrophils**,

- other leukocytes, including **monocytes/macrophages**, **mast cells** and **epithelial cells**, can also generate cathelicidin,
  - in response to cytokines,
  - pathogen-associated molecular patterns (PAMPs)
  - tissue injury (DAMPS)
- chemotactic for various leukocytes including
  - neutrophils, monocytes, mast cells, T cells, and DCs
- Can also induce activation of other cells, including
  - monocytes,
  - macrophages, DCs
  - mast cells,
  - keratinocytes,
  - endothelial
  - epithelial cells

Lactoferrin

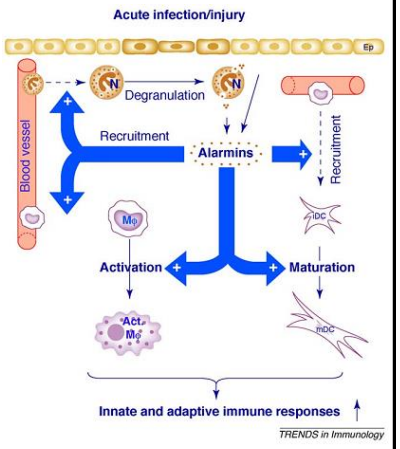
- A **glycoprotein** that belongs to the **transferrin family** of iron-binding proteins
- originally isolated from **milk** and shown to exhibit **antimicrobial** activity based on binding microbial **LPS**, **glycosaminoglycans** and other **surface receptors**
- present in saliva, tears, milk (high concentration), and colostrum (highest concentration)
- **Neutrophils** are an important source of lactoferrin present in **secondary granules**

- not only activates innate immunity, but also, stimulates **DCs**
- lactoferrin can activate the **TLR4** pathway
- Whether lactoferrin is **pro- or anti-inflammatory** is also **controversial**.
  - Oral administration of lactoferrin **reduces colon inflammation** by increasing levels of **IL-10** and **IL-4** and reducing levels of TNF, IL-6 and IL-1.
  - However, it has been also reported that it activates both macrophages and DCs, increasing their production of pro-inflammatory cytokines
  - It also activates the **enterogastric epithelium**, inducing the production of cytokines such as **IL-18** and **type I IFN**, thus stimulating the immune system located beneath the apical surface of the enterocytes.

High-mobility group box-1 protein (HMGB1)

- member of the **HMG superfamily**
- **non-histone chromosomal binding protein** that is normally located in the nucleus where it regulates chromosome **stability** and the **transcription** of certain genes
- is **released extra-cellularly** as a result of loss of membrane integrity upon necrosis of nucleated cells
- **Mononuclear leukocytes** can also secrete HMGB1 in response to PAMPs or pro-inflammatory cytokines
- Extracellular HMGB1 has **antibacterial** activity
- induces both the migration and activation of **DCs**
- HMGB1-induce **NF-kB** activation and cytokine production in phagocytes

- the activation of leukocytes, including DCs, appears to be mediated by multiple receptors including **RAGE** and **TLR2**, **4** and **9**.
- HMGB1 released by **dying tumor cells** has been shown to **enhance anti-tumor immune** responses by triggering **TLR4**-**expressing DCs**



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