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 TGFβ 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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<th>Bioactive Activins</th>
<th>Non-active Activins</th>
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<td>Activin A</td>
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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 ongoing or established inflammatory and immune processes.

• 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.

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**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**

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• 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

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• Alarmins are present in cells, such as **leukocytes** and **epithelial cells** 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)
  - chemoattract 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

**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
- 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)**
- 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**
References