

Interferons in Antiviral Defence

Hans Vilu / 13 slides / Target 4:50 / Limit 5:00

01 Interferons in Antiviral Defence

0:00-0:03

- **Opening.** Interferons in antiviral defence.

02 Interferons: an early warning

0:03-0:18

- **What they are.** Cytokines central to antiviral defence.
- **Main roles.** Induce an antiviral state and coordinate immune-cell activity.
- **Key distinction.** Interferons deliver the signal; responding cells produce the antiviral effectors. They do not directly neutralise viruses.

03 Analogy

0:18-0:56

- **Houses.** Airway epithelial cells; each contains a workshop, the cell's protein-making machinery.
- **Virus.** Enters a house and hijacks the workshop to make viral proteins.
- **Alarm.** The infected cell releases type I interferon; nearby cells prepare defences that make their machinery harder to exploit.
- **Patrol.** Type I interferon also primes NK cells. It is not a kill order: NK cells check activating and inhibitory signals before killing a target.

04 What interferons look like

0:56-1:14

- **Alpha and beta.** Each is a single protein chain.
- **Gamma.** Functions as a dimer: two protein chains, shown in different colours.
- **Reading the image.** Distinct proteins, not stages of one molecule. Lambda is not shown.

05 Three types, different main roles

1:14-1:43

- **Total.** 21 distinct human interferon proteins, grouped into three types by their receptor complexes.
- **Type I: 16.** Includes alpha and beta. Many cells produce them; plasmacytoid dendritic cells are strong alpha producers. Broad antiviral protection.
- **Type II: 1.** Gamma, mainly from NK and activated T cells. Activates macrophages and strengthens cellular immunity.
- **Type III: 4.** Lambda interferons. Antiviral protection mainly at epithelial barriers.

06 Detect the viral material

1:43-2:15

- **Endosomes.** Toll-like receptors detect viral nucleic acids.
- **Cytoplasm.** RIG-I and MDA5 recognise viral RNA and signal through MAVS.
- **Nucleus.** Transcription factors, including IRF3 and IRF7, drive interferon gene expression.
- **Outcome.** Interferon production and release. Receiving the interferon signal is a separate pathway.

07 Turn the warning into a response

2:15-2:44

- **Receive.** Type I interferon binds IFNAR and activates JAK-STAT signalling.
- **Respond.** Activated STAT proteins enter the nucleus and help switch on interferon-stimulated genes; antiviral protein production increases.
- **Where it acts.** Autocrine = same cell. Paracrine = nearby cells.

08 A signal needs a matching receptor

2:44-3:04

- **Left: gamma.** Interferon gamma contacts host receptor-binding chains on both sides.
- **Right: alpha.** Interferon alpha is shown with only one receptor chain.
- **Important limit.** These are partial binding complexes, not complete membrane-spanning receptors. The longer picture guide is in the backup section.

09 Make replication more difficult

3:04-3:44

- **PKR.** Viral double-stranded RNA activates PKR. PKR phosphorylates eIF2-alpha, inhibiting translation initiation and reducing protein production.
- **OAS and RNase L.** Double-stranded RNA activates OAS, which makes 2-5A. This activates RNase L, causing RNA breakdown.
- **Preparation versus activation.** Interferon increases the availability of these defences; viral RNA helps trigger their action.
- **Trade-off.** Neither mechanism is perfectly virus-selective: host protein synthesis and RNA can also be affected.

10 Protection also needs immune cells

3:44-4:10

- **Type I.** Enhances NK-cell responses and increases MHC class I expression.
- **Recognition differs.** MHC I presents intracellular peptides to CD8 T cells. NK cells instead integrate activating and inhibitory target-cell signals.
- **Type II.** Gamma activates macrophages, strengthening their ability to kill ingested microbes.

11 A virus can intercept the warning

4:10-4:32

- **Blue.** C4R, a protein from ectromelia virus, which causes mousepox.
- **Red.** Interferon gamma, trapped by the viral protein.
- **Result.** Gamma cannot reach its normal receptor: the virus intercepts the warning signal.

12 Summary

4:32-4:48

- **Sequence.** Cells detect infection; interferons transmit the warning; responding cells restrict viral replication.
- **Benefit.** Buys time for adaptive immunity.
- **Balance.** The response needs control: persistent signalling can damage tissue.

13 Thank you

4:48-4:50

- **Close.** Thank you.

Just in case

Slide 2 / Interferons: an early warning

The signal is not the defence itself

What does interferon actually do?

- It binds a receptor and changes gene expression in the responding cell. The cell then produces proteins that make viral replication more difficult. The interferon is the instruction; those proteins carry out much of the antiviral work.

What does an antiviral state mean?

- A cell has activated a set of defences that makes it harder for a virus to use it. This is not a physical shield, and it does not guarantee that the cell cannot become infected.

Why is this useful early?

- A warning can reach nearby cells before the virus does. They can prepare while the more specific adaptive response is still developing.

Slide 3 / Analogy

- Airway epithelial cells: ordinary cells lining the nose, windpipe and bronchi, including ciliated cells. Infected and nearby uninfected cells can respond to interferon. This is the clearest neighbourhood example for a respiratory virus; type I and type III interferons can both contribute.
- Skin keratinocytes: the main cells of the epidermis. They can participate in local interferon responses during viral infection; skin is another possible neighbourhood.
- Fibroblasts: connective-tissue cells beneath epithelial surfaces that make extracellular matrix. They can respond to type I interferon and develop antiviral defences. They are not immune patrol cells.
- Intestinal epithelial cells: cells lining the gut. They are another useful neighbourhood example, but type III interferon is particularly important here; do not imply that every tissue relies equally on type I interferon.
- The workshop means host-cell machinery, especially ribosomes: viruses need the cell's ribosomes to translate viral messenger RNA into proteins. They also use cellular energy and building materials. Some viruses encode their own genome-copying enzymes, so not every replication step is performed by a host enzyme.
- Interferon is protective through signalling, not by directly attacking free virus particles. Responding cells make antiviral proteins, and NK cells assess activating and inhibitory target-cell signals before killing. The warning can act on the producing cell as well as its neighbours.

Keep each part of the analogy separate

House versus workshop

- The house is the whole cell. The workshop is machinery inside it, especially ribosomes. A virus brings genetic instructions and relies on the cell to make viral proteins; it does not turn the whole cell into a different kind of object.

What do the neighbours do?

- They respond to interferon by preparing antiviral proteins. These can interfere with protein production or promote RNA breakdown. The alarm does not simply lock a door and prevent all viral entry.

Why does the patrol check another house?

- The tissue can contain more than one infected or stressed cell. NK cells assess each potential target using activating and inhibitory signals; they do not necessarily travel straight to the cell that released interferon. Hearing an alarm alone does not mark a cell for killing.

Slide 4 / What interferons look like

What the different shapes tell you

One chain or two?

- Alpha and beta are each shown as one folded polypeptide chain. Functional gamma consists of two chains associated as a dimer. Two differently coloured parts do not mean two different interferon types.

Why does shape matter?

- A protein's folded surface determines which receptor surfaces it can bind. These structures help explain molecular recognition; they are not pictures of interferon physically attacking a virus.

What are we actually looking at?

- These are structure-based molecular illustrations, not microscope photographs. Their colours are visual labels, not the natural colours of the proteins. Lambda is not included in this image.

Molecular illustrations

Slide 5 / Three types, different main roles

- The total of 21 counts distinct mature human interferon proteins: 16 type I, one type II and four type III. It is not a count of genes or of all interferons across animal species.
- Type I: 12 distinct alpha proteins plus beta, epsilon, kappa and omega. The 13 alpha genes include IFNA1 and IFNA13, which encode the same mature protein. This is why gene-based lists may give 17 type I interferons and 22 overall.
- Type II is gamma. Type III comprises lambda1, lambda2, lambda3 and lambda4; not everyone has a functional IFNL4 allele. The count describes the human repertoire, not what every person or cell produces.

Human interferon count and receptor classification / Discovery of IFNL4

Three kinds of message, not three stages

Type I: a broad antiviral warning

- Alpha and beta are the main examples in this talk. Many cell types can respond to them, and plasmacytoid dendritic cells are particularly strong alpha producers. Other type I members also exist; alpha and beta are not the entire group.

Type II: strengthen immune-cell activity

- Gamma is mainly produced by NK cells and activated T cells. A major effect is to activate macrophages so they become better at killing microbes they have engulfed. Gamma is still a signal, not the patrol cell itself.

Type III: an alarm focused on barriers

- Lambda 1-4 induces an antiviral programme similar to type I. Its receptor is more restricted in distribution, so responses are especially important in epithelial tissues such as the airway and intestine.

What does the total of 21 count?

- Distinct mature human interferon proteins: 16 type I, one type II and four type III. This is not a gene count. The detailed counting convention is retained in the backup notes.

What the simplified labels mean

- **Mainly alpha and beta.** These are the type I interferons emphasised in this talk, not the whole type I group. The group also includes epsilon, kappa and omega.
- **Lambda 1-4.** Type III consists of four lambda interferons. Its antiviral signalling resembles type I, but its receptor distribution concentrates responses at epithelial barriers.
- **All three types are signals.** Type I is the broad antiviral alarm; type III is a more barrier-focused alarm. Type II, gamma, particularly activates macrophages and cellular immunity. Gamma is a message, not the NK-cell patrol or an intracellular weapon.
- **Keep the main talk simple.** Receptor -> JAK-STAT -> antiviral genes is an accurate overview. The molecular detail below is backup for questions, not extra material to recite during the five-minute talk.

Slide 6 / Detect the viral material

From viral material to an interferon warning

1. A sensor recognises a molecular pattern

- The sensor does not recognise a virus by its overall appearance. It binds particular nucleic-acid features, such as certain double-stranded RNA structures, in a particular cellular compartment.

2. A relay carries the information

- RIG-I and MDA5 signal through MAVS. MAVS then helps activate downstream signalling proteins. The original viral RNA does not have to travel to the nucleus and switch on interferon genes itself. Toll-like receptors use different adaptors, not MAVS.

3. Transcription factors act on genes

- IRF3 and IRF7 help regulate interferon gene transcription in the nucleus. They are gene-control proteins, not forms of interferon. The cell subsequently translates the interferon messenger RNA and secretes the resulting protein.

The boundary between slides 6 and 7

- Slide 6: a cell detects viral material and produces interferon. Slide 7: a cell detects that interferon through its surface receptor and prepares defences. The same cell can participate in both processes.

MAVS signalling

How the cell detects a virus

- **1. Detect unusual nucleic acids.** The cell recognises molecular features associated with viruses, rather than seeing a whole virus as an object. Endosomal Toll-like receptors recognise particular RNA or DNA patterns; RIG-I and MDA5 recognise viral RNA in the cytosol.
- **2. Pass the detection signal onward.** RIG-I and MDA5 signal through MAVS, an adaptor associated with the outer mitochondrial membrane. MAVS is a relay, not an interferon or the molecule that directly detects RNA. Toll-like receptors use other adaptors, so not every detection route passes through MAVS.
- **3. Activate gene-control proteins.** Downstream signalling activates transcription factors, including IRF3 and IRF7. They help drive interferon gene transcription in the nucleus. They are not interferons themselves.
- **4. Make and release the warning.** Interferon messenger RNA is translated into protein, which is secreted. The interferon can then signal to its producing cell and neighbouring cells.
- **The distinction to remember.** Detection makes the interferon signal. The IFNAR/JAK-STAT pathway on the next slide receives that signal. Do not treat RIG-I, MAVS and JAK-STAT as one uninterrupted receptor pathway.

RIG-I and MDA5: RNA recognition / MAVS: the signalling adaptor

Slide 7 / Turn the warning into a response

How does the signal actually travel?

It is a relay, not one molecule making the entire journey

- Interferon stays outside the cell while the message is passed through different proteins inside it. Some steps involve binding or phosphorylation; other steps involve proteins physically moving to a new location.

Follow the message through the cell

1. **Outside the cell.** Interferon moves through extracellular fluid and binds its receptor on the cell surface.

2. **At the membrane.** Binding brings the receptor chains into an active arrangement. JAK enzymes attached to their intracellular parts become activated. Interferon does not cross the membrane with the signal.
3. **In the cytoplasm.** JAKs phosphorylate STAT proteins. In the canonical type I pathway, STAT1 and STAT2 associate with IRF9 to form the ISGF3 complex.
4. **Through a nuclear pore.** Nuclear-transport proteins help activated STAT-containing complexes pass through the nuclear envelope into the nucleus. This part involves actual movement of proteins.
5. **Inside the nucleus.** The complexes bind regulatory DNA sequences and promote transcription of interferon-stimulated genes. The genes stay in place; their activity changes.

How do STATs get through the nuclear envelope?

- The envelope contains nuclear pore complexes: selective gateways, not permanent holes admitting everything. Transport proteins called importins recognise appropriate features of the activated STAT complex and help carry it through a pore. You do not need the importin subtype names for the spoken explanation.

What happens after genes are switched on?

- The cell transcribes those genes into messenger RNA. The RNA leaves the nucleus and ribosomes translate it into proteins. Those proteins, including PKR and OAS, help produce the antiviral state.

One distinction worth remembering

- The interferon molecule does not travel from outside the cell to its DNA. Information is relayed; STAT-containing complexes are among the molecules that physically enter the nucleus.

Interferon-activated STAT nuclear import / STAT2-IRF9 and ISGF3

JAK-STAT, step by step

- **The main idea.** A message outside the cell changes gene expression in the nucleus. JAK means Janus kinase; STAT means signal transducer and activator of transcription. The steps here describe the canonical type I interferon pathway.
- **1. Interferon arrives outside the cell.** IFN-alpha or IFN-beta carries an antiviral warning. The interferon itself does not need to enter the cell or travel to its DNA.
- **2. It binds IFNAR.** The type I interferon receptor has two different chains: IFNAR1 and IFNAR2. Interferon binds outside the cell and helps organise an active receptor complex.
- **3. Receptor-associated JAKs activate inside.** TYK2 is associated with IFNAR1, and JAK1 with IFNAR2. Both are enzymes of the Janus kinase family. They transfer the outside binding event into intracellular signalling through phosphorylation.
- **4. STAT1 and STAT2 are phosphorylated.** The activated JAKs phosphorylate STAT1 and STAT2. Phosphorylation means adding a phosphate group; here it enables the STAT proteins to participate in the active signalling complex.

- **5. STAT1, STAT2 and IRF9 form ISGF3.** ISGF3 means interferon-stimulated gene factor 3. It is the name of a three-protein complex, not a fourth protein added to the others: STAT1 + STAT2 + IRF9 = ISGF3. IRF9 is distinct from the IRF3 and IRF7 involved in interferon production.
- **6. The complex acts on DNA in the nucleus.** ISGF3 binds DNA sequences called interferon-stimulated response elements, or ISREs, and promotes transcription of many interferon-stimulated genes, or ISGs. ISGF3 is a protein complex; an ISRE is a DNA sequence; an ISG is a gene.
- **7. Antiviral proteins become more available.** The resulting messenger RNAs are translated into proteins, including PKR and OAS. These help the cell restrict viral replication. Interferon prepares the defences; viral RNA can provide an additional activation trigger.
- **Not identical for every interferon.** Type III uses a different receptor but a similar STAT1-STAT2-IRF9 programme. Type II gamma mainly activates STAT1 homodimers through its own receptor. Do not apply the IFNAR pathway unchanged to gamma.

IFN-alpha/beta -> IFNAR1 + IFNAR2 -> JAK1 + TYK2 -> STAT1 + STAT2 + IRF9 (ISGF3) -> ISRE binding -> ISG transcription -> antiviral proteins

STAT2-IRF9 structure and the ISGF3 complex / Interferon-induced ISGF3 gene control

Slide 8 / A signal needs a matching receptor

Reading the pictures, step by step

What are the coloured blobs?

- These are magnified 3D models of proteins, not pictures of whole cells. The small spheres represent atoms. The colours have been added to distinguish the proteins; they are not their natural colours.

Left picture: interferon gamma

- The orange and pink-red parts intertwined in the middle are interferon gamma. They are its two protein chains, together forming one functional dimer. The blue pieces on either side are the outside, interferon-binding parts of the cell's receptor. They are not extra interferons and are not virus proteins.

Right picture: interferon alpha

- The coral-red part on the right is interferon alpha. The elongated blue part on the left is one receptor component, called IFNAR2. Here alpha is a single protein chain. The picture shows it touching the receptor at the surfaces where they bind.

What is the receptor doing?

- A receptor is the cell's receiver for a particular signal. In a living cell, the complete receptor complex sits in the cell membrane, with a binding region facing outside. Interferon arrives outside the cell and attaches to a compatible receptor: the message has reached its receiver.

What happens after they bind?

- Binding helps organise the receptor complex so that associated proteins inside the cell can start signalling. The JAK-STAT pathway then changes gene expression. Alpha promotes an antiviral programme; gamma strongly activates immune functions, especially in macrophages. Interferon does not have to enter the nucleus and switch genes on itself.

What is missing from these pictures?

- The cell membrane, the inside of the cell and the full set of receptor components are not shown. Alpha also needs another receptor chain, IFNAR1, absent from this image. Gamma likewise needs additional signalling receptor chains. These images show the binding contact, not the entire working signalling system.

The simple meaning

- On this slide, orange/red = the interferon message, and blue = the cell's receiver. Their contact starts a response inside the cell; this is not a picture of a virus being killed.

[Illustration guide](#) / [Gamma-receptor structure](#) / [Alpha-receptor structure](#)

Slide 9 / Make replication more difficult

Preparing a defence is different from activating it

Why are two signals involved?

- Interferon increases the availability of defensive proteins. Viral double-stranded RNA can then activate PKR and OAS. An uninfected neighbour can therefore prepare before it encounters the viral trigger.

PKR: interfere with starting protein synthesis

- PKR is a kinase: it adds phosphate groups to proteins. Its important target here is eIF2-alpha, part of the machinery that initiates translation. Phosphorylation interferes with efficient initiation, so the cell makes fewer proteins. PKR does not directly chop up a virus.

OAS: make the signal that activates the RNA cutter

- OAS uses ATP to make 2-5A. The 2-5A activates RNase L, and RNase L cleaves RNA. Keep the roles separate: OAS makes the messenger; RNase L is the RNA-cutting enzyme.

Why can the cell be harmed too?

- Viruses use the host's protein-making machinery, and these defences are not perfectly specific for viral RNA. Inhibiting translation and degrading RNA can therefore disrupt the host cell as well as the virus.

[RNase L activation](#)

PKR and OAS/RNase L, step by step

- **First: prepare, then activate.** Interferon increases the availability of antiviral proteins. Viral double-stranded RNA can then activate PKR and OAS. The interferon is the warning signal, not the enzyme cutting RNA or blocking translation.

- **PKR: slow the protein-making machinery.** Double-stranded RNA activates PKR, a protein kinase. PKR phosphorylates eIF2-alpha, a translation-initiation factor subunit. This interferes with efficient initiation of protein synthesis, so fewer viral proteins can be made. Phosphorylates is more precise than merely saying modifies.
- **OAS: make an activating messenger.** Double-stranded RNA activates OAS, which uses ATP to make short molecules called 2-5A. OAS is not the enzyme that cuts RNA, and 2-5A is a messenger molecule rather than an interferon or protein enzyme.
- **RNase L: cut RNA.** 2-5A activates RNase L. RNase L cleaves RNA, reducing the material available for viral replication and protein production.
- **The cost to the host cell.** These defences are not perfectly selective for viral material. Host translation and RNA can also be affected, which helps explain why an interferon response must be controlled.
- **One-sentence answer.** PKR restricts protein synthesis; OAS makes 2-5A, which activates RNase L to degrade RNA. Together they make the cell harder for a virus to exploit.

RNase L activation by 2-5A

Slide 10 / Protection also needs immune cells

Three immune-cell roles that should not be mixed up

NK cells: an early target check

- NK cells balance activating and inhibitory signals on a potential target. Self MHC I supplies important inhibitory signals. Type I interferon can enhance NK-cell readiness, but it does not identify a particular target or order it to be killed.

CD8 T cells: specific peptide recognition

- MHC I displays peptide fragments from proteins made inside a cell. A CD8 T cell with the appropriate receptor can recognise a viral peptide displayed this way. Increasing MHC I can support this recognition; it does not mean that MHC I universally activates NK cells.

Macrophages: stronger killing of engulfed microbes

- Gamma activates macrophages and improves their antimicrobial functions. The macrophage is the responding cell; gamma is the instruction that changes its behaviour.

Slide 11 / A virus can intercept the warning

The colours now represent a different interaction

What is blue this time?

- C4R is a viral interferon-binding protein, not a normal human receptor. It comes from ectromelia virus, the cause of mousepox. The image does not show a whole virus particle.

What is being trapped?

- The red component is interferon gamma. Binding to the viral protein prevents it from reaching its normal receptor, so the normal downstream message is blocked.

Compare this with slide 8

- Slide 8 shows productive binding to host receptor components. Slide 11 shows interception by a viral protein. A protein binding interferon is not automatically a signalling receptor.

Viral interferon trap

Slide 12 / Summary

Connect the whole story

Detect, signal, respond

- Viral sensing triggers interferon production. Interferon binds a receptor on a responding cell. That cell changes gene expression, restricts viral replication and coordinates help from immune cells.

Why not keep the response at maximum?

- A defence that suppresses protein synthesis, degrades RNA and stimulates immune activity has costs. Persistent or excessive signalling can contribute to tissue injury. The benefit depends on timing, location and control, not just on producing more interferon.

Which names to prioritise for questions

- **First priority: explain the story.** Know the three interferon types and their main roles; cytokine; receptor; antiviral state; autocrine versus paracrine; and why NK cells are the patrol rather than interferon itself.
- **Names visible on slides 6-10.** Be able to give one sentence for TLRs, RIG-I, MDA5, MAVS, IRF3/IRF7, IFNAR, JAK-STAT, PKR, eIF2-alpha, OAS, 2-5A, RNase L, MHC I, CD8 T cells and macrophages. Their role matters more than reciting every expanded acronym.
- **Second priority: the pathway backup.** Recognise IFNAR1/2, JAK1/TYK2, STAT1/2, IRF9, ISGF3, ISRE and ISG. Remember especially that ISGF3 is a protein complex, ISRE a DNA sequence and ISG a gene. These names explain the simplified JAK-STAT arrow; they do not all need to enter the spoken talk.
- **For the molecular pictures.** Dimer means two subunits. Slide 8 shows partial host receptor complexes, not full receptors or viral proteins. Slide 11 is different: C4R is a viral protein trapping gamma. The PDB accession numbers are source identifiers, not useful memorisation targets.
- **Scope.** These priorities follow this presentation; they are not a guarantee of what an examiner will ask. The glossary below supplies the full definitions.

Terms for questions

Core concepts and interferon types

- **Cytokines.** Signalling proteins that allow cells to influence the behaviour of other cells or themselves.
- **Interferons.** Cytokines that induce antiviral defences and regulate immune-cell activity. All three types act as signals; type I is not the only alarm. Type I gives a broad antiviral warning, type III provides a similar barrier-focused warning, and type II particularly strengthens macrophage and cellular immune responses.
- **Type I interferons.** An interferon group that includes alpha and beta and signals through IFNAR. Many cell types can produce type I interferons after viral sensing; plasmacytoid dendritic cells are especially strong alpha producers. Major effects include inducing antiviral genes and supporting immune-cell responses.
- **Type II interferon.** This group contains interferon gamma, produced mainly by NK cells and activated T cells. It signals through its own interferon-gamma receptor and strongly activates macrophages and cellular immunity; it also has antiviral effects. In the analogy, gamma is an activation message sent by the NK-cell patrol, not the patrol or its defence device. Gamma is not a later form of alpha or beta.
- **Type III interferons.** The lambda interferons. They induce antiviral responses through a receptor distinct from IFNAR, with responsiveness concentrated particularly at epithelial barriers such as the airways and intestine. Their effects overlap with type I interferons, but their main target-cell distribution differs.
- **IFN-alpha.** In this talk, alpha means interferon alpha: a group of closely related type I interferon proteins. They signal through IFNAR and help cells prepare antiviral defences.
- **IFN-beta.** Interferon beta is a type I interferon that signals through IFNAR and helps establish antiviral defences. It is a different protein from interferon alpha, not a later stage of it.
- **IFN-gamma.** Interferon gamma is the sole type II interferon. It is a two-chain protein, produced mainly by NK cells and activated T cells, that particularly strengthens macrophage and cellular immune functions.
- **IFN-lambda.** The type III interferons, lambda 1-4. Their antiviral effects are especially important at cell layers lining surfaces such as the airways and gut.
- **Epsilon.** Names of additional type I interferons, alongside alpha and beta. These are distinct proteins, not successive stages of a single interferon.
- **Antiviral state.** An interferon-induced set of cellular defences that restrict viral replication. It prepares the cell to resist exploitation; it does not seal the cell or guarantee that infection cannot occur.
- **Antiviral effectors.** Molecules that carry out an antiviral action, such as PKR limiting translation or RNase L cleaving RNA. In the neighbourhood analogy, these are the internal defence devices; the interferon is the message that helps prepare them.
- **Innate immunity.** Rapid defence using barriers, cellular sensors, phagocytes, NK cells and soluble mediators. Viral detection and the early interferon response are part of innate immunity and help shape the later adaptive response.

- **Adaptive immunity.** Targeted defence involving B and T cells that recognise particular molecular targets. It develops after these cells are activated and can create memory, allowing a faster response when the same threat returns.

Detecting the infection

- **Pattern-recognition receptors.** Innate immune receptors that recognise characteristic microbial molecules or signs of cellular damage. Viral RNA sensors are examples. Unlike antibodies, they do not require a new antigen-specific response to be generated.
- **Toll-like receptors.** A family of pattern-recognition receptors on cell surfaces or in endosomes. Endosomal members involved in viral recognition include TLR3 for double-stranded RNA, TLR7/8 for single-stranded RNA and TLR9 for DNA containing unmethylated CpG motifs.
- **Endosomes.** Small membrane-enclosed compartments that sort material taken into a cell. Some receptors detect viral DNA or RNA there. This is a different location from the cell's internal fluid, where RIG-I and MDA5 act.
- **Cytoplasm.** The cytoplasm is the part of a cell outside the nucleus, including its organelles. The cytosol is its fluid component. RIG-I and MDA5 sense viral RNA in the cytosol, not inside endosomes.
- **RIG-I.** Retinoic acid-inducible gene I. Here the name refers to its protein product, a cytosolic RNA sensor. It recognises particular RNA ends and structures, including short double-stranded RNA with a 5-prime triphosphate, and signals through MAVS to promote interferon production.
- **MDA5.** Melanoma differentiation-associated protein 5. A cytosolic RNA sensor that preferentially recognises long double-stranded RNA and signals through MAVS. Despite its historical name, its role here is viral detection, not melanoma diagnosis.
- **MAVS.** Mitochondrial antiviral-signalling protein. An adaptor associated with the outer mitochondrial membrane that passes signals from activated RIG-I or MDA5 to downstream pathways, eventually activating factors such as IRF3. It relays the signal rather than directly detecting viral RNA.
- **Transcription factors.** Proteins that regulate which genes are transcribed into RNA.
- **IRF3.** Interferon regulatory factor 3. A transcription factor activated downstream of viral-sensing pathways. It enters the nucleus and helps initiate interferon gene transcription, particularly an early IFN-beta response. It is not an interferon itself.
- **IRF7.** Interferon regulatory factor 7. A transcription factor important for type I interferon production and amplification, including IFN-alpha. Its activity helps strengthen the response after viral recognition; it is not an interferon receptor.

RIG-I and MDA5: RNA recognition / MAVS: the signalling adaptor

Receiving the interferon signal

- **Receptor chains.** Proteins that recognise a signal and help initiate a response. The displayed structural views show only parts of the complete signalling assemblies.
- **IFNAR.** The type I interferon receptor, composed of the two receptor chains IFNAR1 and IFNAR2. Binding of alpha or beta initiates signalling through associated JAK kinases and STAT proteins. The alpha binding picture shows the extracellular part of IFNAR2 only, not the complete receptor.

- **JAK-STAT.** A message relay from a receptor to the cell's genes. JAK enzymes activate STAT proteins; STAT-containing complexes then enter the nucleus and help change which genes are used. Interferon itself stays outside the cell.
- **JAK kinases.** Janus kinases: enzymes attached to the inside parts of certain receptors. They add phosphate tags to proteins and help activate STATs after interferon binds. JAKs act inside the receiving cell, not as the interferon message outside it.
- **JAK1.** Janus kinase 1: an enzyme that helps pass a received signal onward by adding phosphate tags to proteins. Here it is attached to the inside part of receptor chain IFNAR2.
- **TYK2.** Tyrosine kinase 2: an enzyme that helps transmit the interferon message inside the cell by adding phosphate tags. It is attached to receptor chain IFNAR1 and works alongside JAK1.
- **STAT proteins.** Signal transducers and activators of transcription: proteins that help carry a received message to the cell's gene-control machinery. Activated STAT-containing complexes enter the nucleus and help control which genes are used.
- **STAT1.** Signal transducer and activator of transcription 1: a protein that helps control which genes are used after a signal arrives. In the main type I response it joins STAT2 and IRF9; in the main type II response two STAT1 proteins pair together.
- **STAT2.** Signal transducer and activator of transcription 2: a protein that joins STAT1 and IRF9 in a three-protein team called ISGF3. This team helps switch on antiviral genes after type I or type III interferon signals.
- **IRF9.** Interferon regulatory factor 9: the part of the STAT1-STAT2-IRF9 team that helps it recognise specific control sites in DNA. It is different from IRF3 and IRF7, which help the cell produce interferon.
- **ISGF3.** Interferon-stimulated gene factor 3: the transcription-factor complex formed by STAT1, STAT2 and IRF9. It is a complex of three proteins, not another individual protein.
- **ISREs.** Interferon-stimulated response elements: particular DNA control sequences that the ISGF3 protein team recognises. Binding there helps switch on interferon-responsive genes. An ISRE is a stretch of DNA, not a protein.
- **Autocrine.** A signal acts on the same cell that produced it.
- **Paracrine.** A signal acts on neighbouring cells.
- **Gene expression.** Use of a gene's information to produce an RNA and, for protein-coding genes, a protein. Interferon signalling changes which genes are expressed and how strongly; it does not change the cell's DNA sequence.
- **Interferon-stimulated genes.** Genes whose expression increases after interferon signalling. Many encode proteins that restrict viral replication or regulate immune responses. Interferon induces these cellular defences; it does not itself perform all of their antiviral actions.
- **Phosphorylation.** Adding a small chemical tag called a phosphate group to a molecule. It can change the molecule's activity or partners, rather than always switching it on. Here, JAKs activate STATs this way, while PKR tagging eIF2-alpha slows protein production.

Antiviral mechanisms

- **Double-stranded RNA.** RNA containing paired complementary strands. Such structures often arise during viral infection and can activate RNA sensors and antiviral effectors. Their recognition depends on features such as length and location; not every double-stranded RNA molecule is viral.

- **PKR.** Protein kinase R: an enzyme activated by certain double-stranded RNA structures. It adds a phosphate tag to eIF2-alpha, slowing the start of protein production. This restricts viral protein production but also affects the cell's own proteins.
- **Protein kinase.** An enzyme that transfers a phosphate group onto a protein, changing its activity or interactions.
- **EIF2-alpha.** One part of eIF2, a protein complex needed to start making proteins. PKR adds a phosphate tag to this part, slowing the recycling of the start-up machinery and reducing protein production. The full name is eukaryotic translation initiation factor 2 alpha.
- **Translation initiation factor.** A protein involved in starting protein synthesis. PKR modifies eIF2-alpha to inhibit this process.
- **OAS.** An enzyme family that makes the small messenger 2-5A from ATP after detecting double-stranded RNA. The messenger activates RNase L, which cuts RNA; OAS does not do the cutting itself. OAS stands for 2-prime,5-prime-oligoadenylate synthetase.
- **ATP.** Adenosine triphosphate. It supplies energy and phosphate groups for many cellular reactions. In this talk it provides the building units for OAS to make 2-5A and the phosphate donated during kinase reactions.
- **2-5A.** Short chains made from ATP by OAS that act as a message inside the cell: they activate the RNA-cutting enzyme RNase L. Their chemical name is 2-prime,5-prime-linked oligoadenylates. They are not interferons or protein enzymes.
- **RNase L.** Ribonuclease L; RNase means an RNA-cleaving enzyme and L refers to its latent state before activation. Binding of 2-5A activates it to cleave RNA, including viral and cellular RNA. It does not specifically recognise viral RNA alone.

RNase L activation by 2-5A

Immune cells and tissue cells

- **Plasmacytoid dendritic cells.** Specialised immune cells that can rapidly produce large amounts of type I interferon, particularly IFN-alpha, after detecting viral nucleic acids. Their name describes their plasma-cell-like appearance; they are not antibody-producing plasma cells.
- **Natural killer cells.** Innate lymphocytes that can kill infected or abnormal cells. They balance activating cues, often linked to cellular stress, against inhibitory cues such as self MHC class I. Type I interferons can enhance readiness, but do not by themselves identify which cell to kill.
- **Activating and inhibitory signals.** NK cells integrate signals that encourage killing with signals that restrain it. Cellular stress can increase activating ligands; self MHC class I supplies important inhibitory signals. The overall balance determines the response.
- **Prime.** Increase an immune cell's readiness to respond. Priming NK cells does not itself identify a target or order its killing.
- **MHC class I.** Major histocompatibility complex class I: surface molecules that display small pieces of proteins made inside a cell. CD8 T cells inspect these pieces for signs of infection. The body's own MHC I also helps restrain NK cells, so these two immune-cell types interpret it differently.
- **CD8 T cells.** T lymphocytes that recognise peptides presented by MHC class I; cytotoxic effector cells can kill infected cells.

- **T cells.** Immune cells that recognise particular molecular targets through specialised receptors. Some coordinate other immune cells; cytotoxic T cells can kill infected cells.
- **B cells.** Immune cells that can develop into antibody-producing cells. Antibodies bind particular targets; they are different from interferons.
- **Cellular immunity.** Defence carried out mainly through immune-cell actions, particularly T-cell responses, rather than through antibodies alone.
- **Phagocytosis.** Taking particles or microbes into a cell by surrounding them with its membrane. Macrophages can then break down and kill material they have taken in.
- **Macrophages.** Immune cells in tissues that take in and break down microbes and debris. They also release signals and show pieces of what they have taken in to T cells. Interferon gamma strengthens their microbe-killing ability.
- **Epithelial barriers.** Layers of cells lining body surfaces and organs, including the airways and intestine.
- **Airway-lining cells.** Ordinary epithelial cells covering the inside of the nose, windpipe and bronchi. They include ciliated cells and can activate antiviral defences in response to type I or type III interferons.
- **Keratinocytes.** The main cells of the skin's outer layer. They form a physical barrier and can participate in local antiviral and interferon responses.
- **Fibroblasts.** Cells that produce much of the supporting material around other cells, including collagen. They can respond to interferon and develop antiviral defences, but are not NK cells or other immune patrol cells.

Structures and viral evasion

- **Protein chain.** A long sequence of amino-acid building blocks linked by peptide bonds. A chain folds into a three-dimensional shape; a working protein can contain one chain or several associated chains.
- **Monomer.** A single molecular subunit. The depicted alpha and beta interferons are single-chain proteins; this contrasts with the two-chain gamma dimer.
- **Dimer.** A molecular assembly of two subunits. Functional interferon gamma contains two protein chains.
- **Homodimers.** A pair of identical protein units associated together. In the main type II interferon pathway, two activated STAT1 proteins form a homodimer.
- **Subunits.** Individual molecular parts of a larger working assembly. For example, eIF2-alpha is one part of the eIF2 protein complex.
- **Protein complexes.** An assembly of molecules working together. For example, STAT1, STAT2 and IRF9 form one protein complex called ISGF3; they do not become a new single protein.
- **Molecular recognition.** Specific binding between compatible molecular surfaces, such as an interferon and its receptor.
- **C4R.** A viral interferon-gamma-binding protein from ectromelia virus. It acts as a soluble decoy, preventing interferon gamma from reaching its normal host receptor.
- **Ectromelia virus.** Ectromelia virus is an orthopoxvirus that causes mousepox. Its C4R protein is the blue viral component in the displayed 3BES complex.

- **Immune-evasion.** Ways a pathogen avoids or inhibits host immune defences; here, trapping an interferon before it can signal.
- **Decoy.** A molecule that catches a signal or binds another molecule without producing the normal useful response. Here the viral protein traps interferon before it reaches a host receptor.
- **Soluble.** Able to exist in fluid rather than remaining anchored in a cell membrane. A soluble viral decoy can catch interferon outside cells.
- **PDB accession numbers.** Protein Data Bank: an archive of experimentally determined molecular structures. Codes such as 1FG9 identify particular structure records, not protein names.

Supporting molecular biology

- **DNA.** Deoxyribonucleic acid: the genetic material of cells and some viruses.
- **RNA.** Ribonucleic acid: used in gene expression and as the genetic material of many viruses.
- **Messenger RNA.** RNA that carries a protein-coding message read by ribosomes during translation. Viral mRNA supplies instructions for making viral proteins.
- **Nucleus.** The membrane-enclosed compartment containing most of a human cell's DNA. Transcription factors act here to regulate gene transcription.
- **Nuclear envelope.** The double membrane surrounding the nucleus. Nuclear pore complexes provide controlled passage across it.
- **Nuclear pore complexes.** Selective protein gateways spanning the nuclear envelope. They control exchange between the cytoplasm and nucleus; transport proteins help large cargoes such as activated STAT complexes pass through them.
- **Importins.** Nuclear-transport proteins that recognise appropriate features on cargo proteins and help move them through nuclear pore complexes into the nucleus.
- **Extracellular fluid.** Fluid outside cells. Secreted interferons move through this fluid to encounter receptors on the same or nearby cells.
- **Ribosomes.** RNA-protein complexes that read messenger RNA and assemble amino acids into proteins. Viruses rely on host ribosomes to make viral proteins; they do not possess their own complete protein-making machinery.
- **Transcription.** Making an RNA copy using instructions in DNA. This is the first main step in using a protein-coding gene; the RNA can subsequently be read to build a protein.
- **Translation.** Building a protein by reading messenger RNA at a ribosome, the cell's protein-making machinery. This is different from transcription, which makes RNA. Viruses rely on this machinery to make viral proteins.
- **Viral replication.** Production of new viral genomes and components inside a host cell.
- **Peptides.** Short chains of amino acids. MHC class I displays peptide fragments from proteins made inside the cell, allowing CD8 T cells to inspect what the cell is producing.
- **Host cell.** A cell used by a virus to produce viral components and new virus particles. Host means the infected organism or its cell, as distinct from the virus.
- **Enzyme.** A biological catalyst that speeds up a reaction. PKR adds phosphate groups, OAS synthesises 2-5A, and RNase L cuts RNA; an interferon instead acts primarily as a signal.

Everyday biological basics

- **Cells.** The smallest living units of the body. Each has an outer membrane and internal machinery; most human cells also have a nucleus containing DNA.
- **Immune cells.** Cells specialised in defending the body, such as NK cells, T cells and macrophages. Ordinary tissue cells can also detect infection and respond to interferons.
- **Immune system.** The body's network of barriers, cells and molecules that recognises and responds to infection and other threats.
- **Immune response.** The actions the body takes after recognising a threat, including sending signals, limiting infection and removing infected cells.
- **Proteins.** Molecules built from chains of amino acids that fold into particular shapes. They perform much of a cell's work, including signalling, detecting messages and carrying out chemical reactions.
- **Amino acid residues.** The building blocks joined together to make proteins. Residue means an amino acid unit once it is incorporated into a chain.
- **Molecules.** A molecule is a group of atoms held together by chemical bonds. Molecular means describing events at this very small scale, such as one protein binding another.
- **Atoms.** The small units of chemical elements, such as carbon or oxygen. Atoms join together to form molecules; the small spheres in the structural pictures represent atoms.
- **Viruses.** Infectious agents containing genetic instructions inside a protective coat, sometimes with an outer membrane. They must use living cells to produce new virus particles. Viral means relating to a virus.
- **Infection.** Infection means an infectious agent has entered and become established in the body or a cell. Here, an infected cell contains a virus using it to reproduce.
- **Antiviral.** Acting against viruses. An antiviral response can limit virus reproduction or spread without necessarily stopping every virus from entering a cell.
- **Microbes.** Microbes are microscopic agents such as bacteria and fungi; the word is also commonly used broadly to include viruses. Antimicrobial means acting against such agents.
- **Tissues.** Groups of cells and surrounding material organised to perform a function, such as the lining of an airway or the skin.
- **Neutralising.** Blocking a virus's ability to infect cells by acting on the virus itself, for example when an antibody blocks attachment. Interferons mainly change the receiving cell's defences instead.

Places inside and around cells

- **Cell surface.** The cell's outer boundary, where surface receptors can encounter messages outside the cell. Their inner parts can connect that encounter to a response inside.
- **Cell membrane.** A thin, flexible boundary made mainly of lipids and proteins. It separates a cell from its surroundings; internal membranes also enclose cell compartments. A membrane-spanning protein crosses this boundary.
- **Intracellular.** Inside a cell. For example, intracellular signalling happens after a receptor has received a message at the cell surface.
- **Extracellular.** Outside cells. Interferons are released into this space and bind the outward-facing parts of receptors.

- **Cellular compartments.** Separate regions inside a cell, often enclosed by membranes, where particular processes happen. Endosomes and the nucleus are examples.
- **Mitochondrial.** Mitochondria are cell structures involved in energy production and other functions. Mitochondrial means relating to them; MAVS can sit on their outer membrane and relay antiviral signals.
- **Bronchi.** The main branching air passages carrying air from the windpipe into the lungs.
- **Ciliated cells.** Cells with tiny moving projections on their surface. In the airways, these projections move mucus and trapped material toward the throat.
- **Epidermis.** The outer cellular layer of the skin, made mainly of keratinocytes.
- **Connective-tissue.** Tissue that supports and connects other body structures. It includes cells such as fibroblasts and the supporting material they produce.
- **Extracellular matrix.** The supporting network of proteins and other molecules outside cells, including collagen. Fibroblasts make many of its components.

Genes and molecular instructions

- **Genes.** Sections of DNA containing instructions for functional products, such as proteins or RNA. Switching a gene on means using its instructions, not moving the gene or changing its DNA sequence.
- **Genetic material.** The stored instructions used to build and run biological systems. Human cells use DNA; viruses can store their instructions in DNA or RNA. A genome is the complete set of genetic material.
- **Nucleic acids.** DNA and RNA: long molecules that store, transmit or help use genetic information. Cells can detect unusual features of viral nucleic acids as signs of infection.
- **Regulatory DNA sequences.** A DNA sequence is an ordered series of DNA building blocks. Regulatory sequences are sites where proteins bind to help control whether, and how strongly, nearby genes are used.
- **Functional allele.** An allele is a version of a gene. A functional allele can produce a working product; not everyone carries a version of IFNL4 that produces functional interferon lambda 4.
- **IFNA1.** Two different human genes whose mature interferon-alpha protein products are identical. They explain why counting alpha genes gives a different total from counting distinct mature alpha proteins.
- **IFNL4.** The gene for interferon lambda 4, a type III interferon. Genetic variation means that not every person produces a functional lambda 4 protein.
- **Encode.** Contain genetic instructions for a particular product. A protein-coding gene supplies the instructions used to make that protein.
- **Mature protein.** A protein in its processed form after necessary steps such as removal of a secretion signal. Different genes can sometimes produce the same mature protein.

What pathway words mean

- **Signalling pathway.** A sequence in which a cell receives information and passes it between molecules to change its behaviour. The same physical molecule does not have to travel through every step.
- **Secretion.** Release of a substance made by a cell into the space outside it. Secreted interferon can reach receptors on the same cell or other cells.

- **Binding.** Molecules attaching to each other through compatible surfaces. Binding interferon to its receptor starts a response; binding it to a viral trap can instead block that response.
 - **Activation.** Making a molecule or cell functionally active or more responsive. This can happen through binding, a chemical change or assembly with other molecules.
 - **Inhibitory.** Reducing or preventing an activity. An inhibitory signal restrains a cell's response; an inhibitor of protein synthesis reduces protein production.
 - **Kinases.** Enzymes that add phosphate groups to other molecules. This changes how the target behaves; it does not always switch the target on. JAKs and PKR are protein kinases.
 - **Phosphate groups.** Small chemical groups containing phosphorus and oxygen. Adding one to a protein can change its shape, interactions or activity, like adding a chemical control tag.
 - **RNA breakdown.** Cutting molecules into smaller pieces. Here, RNase L cuts RNA, disrupting messages and other RNA needed for normal cell functions and virus reproduction.
 - **Adaptors.** In cell signalling, a relay passes information from one molecule to the next. An adaptor is a protein that connects parts of a signalling pathway; it is not necessarily the original sensor or an enzyme.
 - **Downstream.** Later in a signalling sequence. Downstream of a receptor means events triggered after the receptor is activated, not a literal direction inside the cell.
 - **Canonical.** The standard, well-established version of a pathway used to explain its main sequence. Cells can also have variations or additional signalling routes.
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