TLR9. Although these detect nucleic acids and drive type I interferon gene expression, they do not use TRIF (ref. 2). Instead, they use MyD88 to activate the interferon regulatory factor IRF5 (ref. 6), which is related in structure and function to IRF3 and IRF7. A licensing step involving a pLxIS motif had not been found previously in the signalling cascades of TLR7, TLR8 and TLR9.

Immune cells called plasmacytoid dendritic cells express high levels of TLR7 and TLR9, and are crucial to antiviral defences through their production of large amounts of type I interferon. But these cells are also central players in systemic lupus erythematosus[7]. Previous studies of the molecular mechanisms underlying this disease[7,8] have identified a protein called SLC15A4, located on endolysosomal membranes, which transports polypeptides and the amino acid histidine. SLC15A4 has been linked to the activation of TLRs.

To investigate the role of SLC15A4 further, Heinz and colleagues used mass spectrometry to probe for proteins that interact with it. This approach identified the protein TASL, which had previously been little researched. TASL is highly abundant in cells of the innate immune system, and Heinz and colleagues found that it is tethered to endolysosomes through interactions with SLC15A4. The authors' further experiments confirmed that this interaction is specific: SLC15A4 bound TASL in immunoprecipitation tests; however, neither the related protein SLC15A3 nor a mutant version of SLC15A4 interacted with TASL in such assays.

When the authors engineered plasmacytoid dendritic cells and immune cells called monocytes to lack expression of the gene encoding TASL, they found that signalling mediated by TLR7, TLR8 and TLR9 was abolished, and a similar effect was seen when SLC15A4 was absent. Heinz *et al.* went on to demonstrate that TASL acts specifically through IRF5 by finding that the response to TLR7 and TLR9 activation remained intact in immune cells lacking IRF3 or IRF7, but was blocked in cells deficient in TASL or IRF5. However, NF-κB-mediated signalling was unaffected when the pathway acting through TASL was disrupted. Intriguingly, the authors identified a pLxIS motif in TASL, and found evidence that phosphorylation of this motif – by kinases downstream of MyD88 that are associated with NF-κB activation – mediates IRF5 activation.

This discovery elevates TASL to membership of an exclusive circle of IRF-activating adaptor proteins containing pLxIS motifs, of which the other members are TRIF, MAVS and STING (ref. 5). These four proteins together control the type I interferon response induced by nucleic-acid sensing, a picture that has now been completed with the discovery of TASL as the missing pLxIS adaptor of TLR7, TLR8 and TLR9 signalling.

Given that TASL signals to IRF5, but not to IRF3 or IRF7, it will be interesting to determine the structural features required for the differential recruitment of IRF-family members to pLxIS-motif-containing proteins. Although the authors performed preliminary experiments to investigate phosphorylation events in this system, phosphorylation of the pLxIS motif in TASL should be investigated in detail to identify the kinase(s) responsible.

Moreover, it will be interesting to sort out how this newly identified signalling pathway operates in relation to activation of the pathway involving MyD88, which is the key adaptor of TLR7, TLR8 and TLR9 signalling[9]. As has been shown for other signalling cascades triggered by TLRs and involving multiple adaptors, it is possible that MyD88-mediated signalling and the pLxIS licensing step involving TASL emanate sequentially from distinct endolysosomal vesicles at different stages of maturation[2]. Although TASL is not involved in NF-κB activation, the authors found that the expression of certain pro-inflammatory genes was still blocked in TASL-deficient cells, probably because of the associated defect in IRF5 activation. Nonetheless, by offering a way to dampen interferon-mediated autoimmunity in a way that doesn't block the ability to launch an inflammatory defence response, TASL might prove to be a drug target for treating autoimmune diseases that are fuelled by the engagement of TLR7, TLR8 and TLR9.

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Astronomy

# An early start for galactic disks

**Alfred Tiley**

A powerful radio telescope has peered back through time to observe a galaxy that contained a cold, rotating disk of gas not long after the Big Bang – fuelling the debate about when and how disks first formed in galaxies. **See p.269**

Galaxies are immense, gravitationally bound systems composed of stars, dust, gas and invisible 'dark matter'. Understanding how galaxies have formed and grown over time is essential for a more general view of how matter assembles into large structures – a key piece of the puzzle in our efforts to comprehend the Universe. A crucial step towards this goal is to obtain a clear picture of when disk structures first appeared in galaxies. On page 269, Neeleman *et al.*[1] present observations that reveal a massive, rotating disk of cold gas inside a star-forming galaxy only 1.5 billion years after the Big Bang. This is considerably earlier in cosmic history than the times when previously detected gas disks were found to have existed[2].

According to our current understanding of cosmology, the earliest large-scale structures in the Universe were spherical dark-matter 'haloes' that collapsed under their own gravity[3]. Surrounding gas fell into these haloes, subsequently forming stars and, ultimately, galaxies[4]. Haloes and galaxies are thought to have continued to grow together by hierarchical assembly (merging), and through the further accretion of gas and its conversion to stars[5]. Hierarchical assembly is simple, and is thought to be well understood. However, there is still much debate surrounding the exact pathways by which gas accretion and its assembly into stars occurs, and how it relates to the formation of physical and dynamical structures in galaxies over time.

A key component of this mystery is why some galaxies, such as our own star-forming Milky Way, have physical structures dominated by disks of stars and gas (Fig. 1), whereas other, generally older and more quiescent galaxies do not. The answer is probably

**Figure 1 | The dusty spiral galaxy NGC 4414.** Many star-forming galaxies contain disks of dust and gas — here, the dust is visible as dark patches and streaks silhouetted against the starlight. Neeleman *et al.*[1] report the observation of another galaxy disk that existed just 1.5 billion years after the Big Bang, considerably earlier than previously reported disks.

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intimately linked to each galaxy's history of assembly — specifically, to the relative importance of hierarchical merging (which can either promote or destroy disk growth, depending on the circumstances[6,7]) and of growth through gas accretion (among other processes).

Gas accretion is thought to occur through either a hot or cold mode. As the names suggest, the main difference in these modes is whether the gas is hot or cold as it falls towards the centre of a dark-matter halo onto a galaxy. The hot mode of accretion results in galaxy disks forming late, because a considerable amount of time is needed for the accreted gas to cool and eventually settle into a disk. In the cold mode of accretion, the gas instead remains cool as it falls into the halo centre, thus allowing more-rapid disk formation[8].

Determining when disks first emerged in galaxies, and how frequently, should thus provide important insights into how the early assembly of galaxies took place. To do this, disks must be found in progressively more-distant galaxies, so that researchers can probe ever further back in time towards the Big Bang. (The light from more-distant galaxies takes longer to arrive at our Earth-bound telescopes and detectors than does light from closer galaxies, and therefore provides information about the Universe from further back in time.) This requires extremely sensitive instruments that produce high-resolution data. Modern advances in detector and telescope technology, and in instrument design, have enabled the detection of gas disks in massive galaxies that existed around 3 billion years after the Big Bang[2].

To extend observations of gas in galaxies to even earlier periods of cosmic history, Neeleman *et al.* used the Atacama Large Millimeter/submillimeter Array (ALMA), one of the most powerful radio telescopes in the world, situated in the Atacama Desert in northern Chile. The researchers detected light emitted from cold gas in a galaxy from around 12.5 billion years ago. By resolving the light to a scale of 1.3 kiloparsecs (about one-sixth of the distance from our Sun to the centre of the Milky Way[9]), they were able to examine the structure and kinematics of the emitting gas in impressive detail. They then used simple but robust analytical models to show that their observations are consistent with the presence of a rapidly rotating gas disk, spatially coincident with the galaxy's stars and dust.

Neeleman and colleagues' results constitute some of the first observational evidence for the existence of cold gas disks in massive galaxies very soon after the Big Bang, directly establishing that massive gas disks could form 1.5 billion years earlier than previous observations had indicated[2]. The authors' work considerably shifts the observational frontier for the detailed study of spatially resolved gas properties in galaxies to when the Universe was only about one-tenth of its current age.

Their discovery is intriguing when viewed alongside the results of some numerical simulations of galaxy formation, which suggest that disks did not begin to dominate in galaxies of similar mass until the Universe was between 4 billion and 6 billion years old[10,11]. However, it is consistent with the theoretical expectation that cold-mode accretion should be dominant early in the Universe's history[8]. It also ties in with recent, higher-resolution simulations that have seen disks emerge at earlier cosmic epochs[12].

One limitation of the work, when it comes to constraining our theoretical understanding of galaxy formation or testing the differing predictions of numerical simulations, is that the authors consider only one galaxy. Similar observations of many more galaxies from the same epoch are needed before we can determine whether the galaxy studied is representative of the whole population at that time, or whether it is an outlier. Moreover, although the authors' results seem to speak against hot-mode accretion scenarios for early galaxy growth, their data do not explicitly rule out other ways, besides cold-mode accretion, in which cool gas could be efficiently transported to the centres of haloes — for example, through the merging of galaxies and their haloes[7]. Further observational data are required to resolve this issue. Nevertheless, Neeleman and colleagues' findings will excite astronomers, and open up a new epoch of the Universe's history for the study of early galaxy formation.

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