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# Integrin-mediated adhesion complex

## Cooption of signaling systems at the dawn of Metazoa

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The integrin-mediated adhesion machinery is the primary cell-matrix adhesion mechanism in Metazoa. The integrin adhesion complex, which modulates important aspects of the cell physiology, is composed of integrins (alpha and beta subunits) and several scaffolding and signaling proteins. Integrins appeared to be absent in all non-metazoan eukaryotes so-far analyzed, including fungi, plants and choanoflagellates, the sister-group to Metazoa. Thus, integrins and, therefore, the integrin-mediated adhesion and signaling mechanism was considered a metazoan innovation. Recently, a broad comparative genomic analysis including new genome data from several unicellular organisms closely related to fungi and metazoans shattered previous views. The integrin adhesion and signaling complex is not specific to Metazoa, but rather it is present in apusozoans and holozoan protists. Thus, this important signaling and adhesion system predated the origin of Fungi and Metazoa, and was subsequently lost in fungi and choanoflagellates. This finding suggests that cooption played a more important role in the origin of Metazoa than previously believed. Here, we hypothesize that the integrin adhesion was ancestrally involved in signaling.

Both cell adhesion and cell signaling, which are often correlated, are essential mechanisms for metazoan multicellularity.<sup>1</sup> Thus, elucidating the origin and evolution of those processes is key to further our understanding of metazoan origins. It has been inferred that the most ancestral

cell junctions in metazoans are spot adhesion junctions and focal adhesions.<sup>2</sup> The former are important for cell-cell adhesion and are molecularly based on cadherins, coupled with the actin cytoskeleton through catenins. On the other hand, focal adhesions are essential for cell-extracellular matrix (ECM) connection and are molecularly based on the integrin adhesion complex also linked to the actin cytoskeleton.

None of those two-cell adhesion systems are present in fungi or plants, but the analysis of the first genome sequence of a choanoflagellate, a group of single-celled and colony forming flagellates that are the closest relatives to metazoans, showed that cadherins appeared prior to the metazoan divergence. In fact, up to 23 different cadherins were described in the choanoflagellate *Monosiga brevicollis*, some of them structurally homologous to some metazoan cadherins (e.g., protocadherin or FAT) and others with completely new domain arrangements.<sup>3</sup> However, *M. brevicollis* does not have an integrin-mediated adhesion system. This leaves the integrin-mediated adhesion and signaling mechanism as one of the key inventions of the metazoan lineage.<sup>4,5</sup>

Molecular systematics has shown that choanoflagellates are not the only single-celled metazoan relatives. In fact, the opisthokonts are no longer a game of three (Metazoa, Fungi and choanoflagellates), but rather an eukaryotic clade teaming up with an increasing number of poorly known protist lineages, such as nucleariids, ichthyosporeans, filastereans (namely *Capsaspora owczarzaki*

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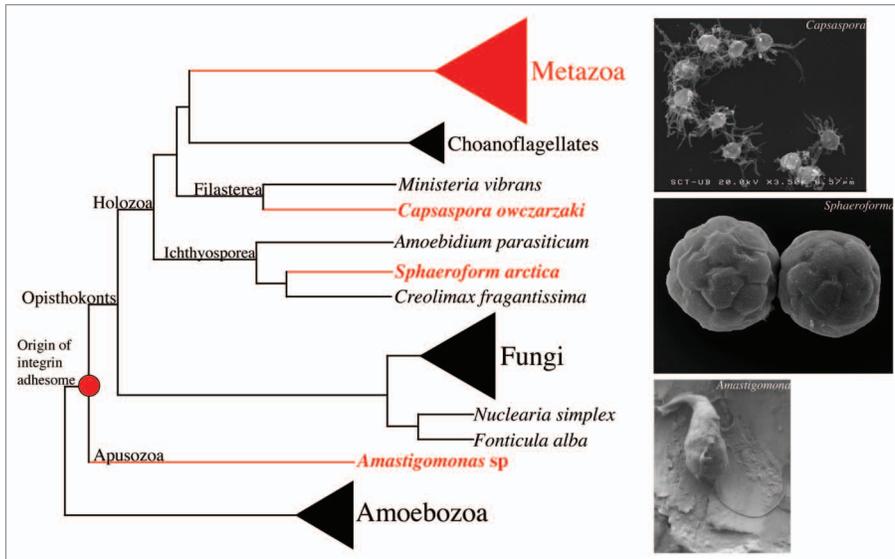
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**Figure 1.** Schematic phylogenetic tree of the opisthokonts showing the putative origin of the integrin adhesion system with the current taxon sampling. Relationships are based on both published and unpublished molecular analyses.<sup>6-10</sup> Taxa in red are the ones encoding a complete integrin-mediated adhesion machinery. In bold taxa with complete genome sequences. Note that the genome of *S. arctica* is currently under way, but the trace data shows integrin hits.

and *Ministeria vibrans*), *Corallochytrium limacisporum* and, very recently, *Fonticula alba* (see Fig. 1).<sup>6-10</sup> That means those lineages should be taken into account when trying to infer the metazoan and fungi “genetic starter kit”. In this regard, the UNICORN initiative aims to obtain the genome sequence of up to eleven protists lineages closely related to both fungi and metazoans.<sup>11</sup> Thanks to this project, the genome sequence of two chytrid fungi (*Allomyces macrogynus* and *Spizellomyces punctatus*), one filasterean (*C. owczarzaki*) and one choanoflagellate (*Proterospongia* sp.) have been obtained and are publicly available. Moreover, the complete genome of one apusozoan (*Amastigomonas* sp.), the putative sister-group of the opisthokonts<sup>10,12</sup> has also been sequenced.

This new information allows useful and taxonomically broader comparative genomic analyses, such as the one recently published by Arnau Sebé-Pedrós et al.<sup>13</sup> in which the repertoire of the different components of the integrin adhesome in opisthokonts and eukaryotes in general was investigated. The findings of Sebé-Pedrós are indeed unexpected, since a whole integrin-mediated machinery was found in two non-metazoan lineages, the filasterean *C. owczarzaki* and the apusozoan *Amastigomonas* sp. (see Fig. 1). That

the integrin-mediated complex is present in *C. owczarzaki* is by itself interesting enough, implying (1) that integrins are not exclusive to Metazoa and (2) that choanoflagellates lost such an important adhesion and signaling mechanisms. However, the most surprising finding is that the genome of the single-celled apusozoan *Amastigomonas* sp., which is not an opisthokont, also encodes the full repertoire (except for the two associated tyrosine kinases) of the integrin-mediated adhesion complex. These findings have large evolutionary implications. They not only take the integrin exclusivity out of metazoans, but also indicate that fungi (which comprise several species with complex multicellularity) secondarily lost this important cell adhesion and signaling machinery. Moreover, the finding that the origin of integrins is ancient means that the two most important metazoan cell adhesion mechanisms (cadherins and integrins) were already present in pre-metazoan lineages, and they were probably coopted for new functions in metazoans.

Undoubtedly, the presence of integrins in those unicellular organisms opens new and challenging questions. The first one, the actual role that this integrin machinery is playing in those single-celled organisms. Is the integrin machinery involved

in sensing the extracellular environment? Such is the case, for example, of cadherins in choanoflagellates, which have been proposed to be involved in the response to the extracellular environment, as bacterial prey capture.<sup>3</sup> Another question is whether integrins are present in other opisthokont lineages, such as ichthyosporan or nucleariids or *Fonticula alba* (which are the sister-group to Fungi). In this regard, the genome data of the remaining taxa to be sequenced by the UNICORN initiative (namely *F. alba*, the ichthyosporans *Sphaeroforma arctica* and *Amoebidium parasiticum* and the free-living filasterean *M. vibrans*) will surely help unravel the evolutionary history of such important cell adhesion machinery.

Actually, a quick look at the current genome trace data of one ichthyosporan, *S. arctica*, whose genome is currently being sequenced, shows strong hits to integrins, suggesting that ichthyosporans most probably also encode the integrin adhesion machinery. That means integrins are found in very different functional contexts, from single-celled amoeba endosymbiont crawlers (such as *C. owczarzaki*), to marine free-living flagellates (such as *Amastigomonas* sp.), to colony-forming fish and arthropod parasites (such as the ichthyosporan *S. arctica*), to fully multicellular eukaryotes (such as Metazoa) (see the Fig. 1). To us, this capacity to work in such different contexts suggests that integrins most probably had an ancestral role in signaling, for example in sensing the environment to modulate cell physiology and growth. The fact that the IPP signaling module is as ancient as integrins (it is also present in apusozoans, reviewed in ref. 13), and that the two tyrosine kinases associated with the integrin machinery (FAK and C-Src) were already present in the common ancestor of *C. owczarzaki*, choanoflagellates and Metazoa, seem to back up the signaling role of the ancestral integrins. The current cell-extracellular matrix role of the integrin complex in metazoans may have appeared by co-option, although we can not rule out the possibility that integrins in pre-metazoans played a cell adhesion role in, for example, the colony-forming ichthyosporans. In any case, functional analyses to elucidate the current role of the integrin adhesion

system in *C. owczarzaki*, *S. arctica* or *Amastigomonas* sp., will surely be crucial to fully answer these new open questions.

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