## From the archive

**An observation of aggressive anemones, and the overzealous celebration of Louis Pasteur's 100th birthday.**

### 50 years ago

Aggressiveness is not a trait very obviously associated with sea anemones. Yet Francis ... has ... found overt aggression in the Californian anemone *Anthopleura elegantissima* ... A most striking feature of the spatial distribution of the anemones is that they live in clumps ... of the same colour pattern and of the same sex. The anemones are known to reproduce asexually ... so that the different clumps are almost certainly groups of genetically identical individuals (clones). When taken into the laboratory and mixed together, the anemones segregate back into their clones. Contact between genetically different individuals was found to lead to ... aggressive behaviours, one or both animals being damaged in the process ... *Anthopleura* shows this behaviour neither to species upon which it preys (for example, small mussels) nor to its predators (for example, sea slugs) and the curious clumped distribution of these anemones ... would seem to be attributable to their own aggressive behaviour.
**From *Nature* 25 May 1973**

### 100 years ago

France is occupied this week with the celebration of the centenary of Pasteur's birth. We, in Great Britain ... are very proud of Shakespeare ... yet our national gratitude toward Pasteur ... ought to be even more certain than our gratitude toward Shakespeare ... Things have been done better in France. It is possible that the worship of Pasteur has gone too far, in the "filming" of him ... Men and women of science may or may not stand the test of acting; but they are not intended for "filming." Take some names at random — Newton, Darwin, Lister, Kelvin: films "featuring" them would be nightmares. Besides, the whole meaning and beauty of their work would be left out. Their work began in them, but did not stop there ... So with Pasteur's work: he founded his kingdom in every country of the world.
**From *Nature* 26 May 1923**


into the uterus, but did not develop further.

In the third paper, Mazid and colleagues[3] sought to derive human totipotent cells, beginning with cultures of human pluripotent stem cells, which represent a later stage of embryonic development than do mouse embryonic stem cells. Through a series of manipulations of the culture conditions, the authors gradually wound back the developmental clock *in vitro* to obtain cultures that were enriched in cells similar to those of the eight-cell human embryo (thought to represent a totipotent stage).

These cells — which could be purified from mixed cultures by using a fluorescent reporter specific to the eight-cell stage — had molecular characteristics consistent with the totipotent state in human embryos. Like their mouse counterparts, these cells could also give rise to extra-embryonic lineages as well as to the tissues of the embryo proper in interspecies chimaeras formed after injection into host mouse embryos. The cells differentiated into trophoblast cells and blastoids *in vitro*, and, when injected into immunologically deficient adult mice, produced benign growths called teratomas that contained trophoblast tissue.

All the culture systems described here contain a mix of cell types, and it will be important to define clearly the key biological properties of their main subpopulations. Moreover, the cells have not yet passed the most rigorous test of totipotency: the ability to generate a new organism independently of other cell types. And although careful examination of the molecular profiles of the cultured totipotent cells found them to be a close replica of their embryonic counterparts, undiscovered 'epigenetic' abnormalities might compromise their developmental capacity. For example, it could be that the absence of maternal-effect gene products (transcripts that come from the egg and are required for normal development[6]) somehow interferes with the development of the cultured totipotent cells.

Given the progress now reported, however, it seems likely that such limitations will eventually be overcome. Will it then be possible, using *in vitro* technology alone, to produce viable embryos directly from induced pluripotent stem cells derived from living animals, including humans? If embryo-like structures or blastoids produced from cultured totipotent cells are eventually endowed with the capacity to undergo normal development to term, broad new horizons in embryological research — along with new ethical challenges — will lie ahead.

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1. Hu, Y. *et al. Nature* **617**, 792–797 (2023).
2. Yang, M. *et al. Cell Stem Cell* **29**, 400–418 (2022).
3. Mazid, M. A. *et al. Nature* **605**, 315–324 (2022).
4. Baker, C. L. & Pera, M. F. *Cell Stem Cell* **22**, 25–34 (2018).
5. Posfai, E. *et al. Nature Cell Biol.* **23**, 49–60 (2021).
6. Mitchell, L. E. *HGG Adv.* **3**, 100067 (2022).

**The author declares no competing interests.**
**This article was published online on 17 May 2023.**

Cancer

# Molecular basis for muscle loss that causes cachexia

**Laura Antonio-Herrera & Andreas Bergthaler**

Muscle loss during chronic disease is a life-threatening condition for which there is no effective treatment. The identification of an underlying molecular mechanism might offer new therapeutic targets. **See p.827**

Loss of body weight is common in people who have chronic inflammatory conditions such as cancer, cardiovascular disease, infections and metabolic disorders. Such individuals show a decrease in appetite and loss of skeletal muscle and fat mass — a manifestation of a multi-organ syndrome called cachexia[1]. People with cancer and cachexia are at higher risk of a poor response to treatment and death than are those without cachexia[2]. Efforts to alleviate cachexia include nutritional interventions, exercise regimes and pharmacological targeting of suspected mediating molecules[2]. However, interventions against current molecular targets are insufficient to reverse this muscle loss[3–5]. Bilgic *et al.*[6] describe on page 827 a molecular mechanism involved in muscle degradation that offers new therapeutic targets for tackling cachexia.

Muscle mass is maintained by a balance between protein synthesis and degradation. Cachexia-related muscle loss, or atrophy, is

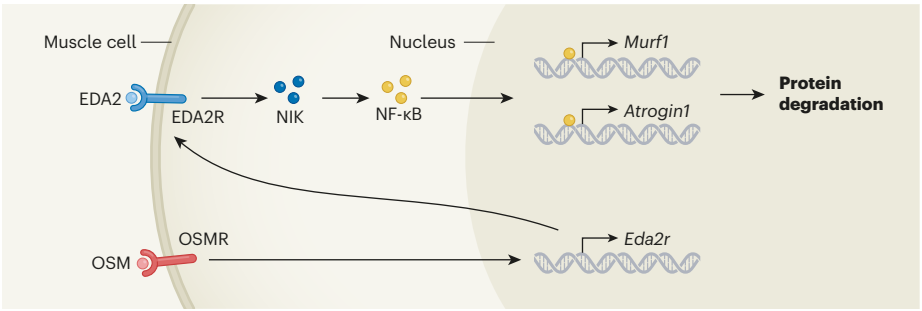


**Figure 1 | A pathway involved in muscle loss.** Bilgic *et al.*[6] investigated factors associated with muscle wasting, a symptom of a condition called cachexia that can develop during cancer. The authors found that the receptor protein EDA2R is strongly expressed in muscle biopsies obtained from people with muscle wasting and in animal models of cachexia. They report that interaction of the EDA2 protein with EDA2R stabilizes the enzyme NIK, enabling activation of a pathway mediated by the protein NF-κB. This drives expression of the genes *Atrogin1* and *Murf1*, which encode enzymes that mediate the breakdown of muscle protein. Interaction between the immune-signalling protein OSM and its receptor protein OSMR can promote muscle wasting directly and drive expression of the gene encoding EDA2R.

characterized by excessive protein degradation and a reduction in protein synthesis. A combination of dietary and exercise regimes is thought to promote protein synthesis[7,8]. However, to prevent excessive protein breakdown, it is necessary to identify the molecules involved in the associated inflammation, and the hubs at which the molecular signalling cascades converge.

Proinflammatory molecules called cytokines, such as TNF-α, IL-6 and TWEAK, have been implicated in muscle loss through their activation of the downstream transcription-factor protein NF-κB. This pathway triggers the expression and activation of protein-degrading (proteolytic) enzymes[2]. In animal models of cachexia associated with cancer, inhibition of these cytokines or their receptors can alleviate muscle loss. However, such strategies have proved insufficient in clinical studies[3–5], hinting at the involvement of other mediators.

Bilgic *et al.* reveal that a signalling pathway consisting of the protein EDA (specifically, a version of this protein termed EDA2, or EDA-A2), its receptor EDA2R, and the downstream signalling molecules NIK and NF-κB, is responsible for muscle atrophy in animal models of cancer-associated cachexia (Fig. 1). The authors report that, in mice and humans, the gene encoding EDA2R is expressed at higher than normal levels in skeletal muscle across various diseases with muscle atrophy. The addition of EDA to mouse or human-derived muscle cells (myotubes) *in vitro* led to a reduction in their size and induced the expression of genes involved in muscle atrophy. Similarly, driving higher expression of EDA2, through intramuscular injection of mice with a virus that expresses EDA2, resulted in muscle loss at the injection site.

The authors show that EDA2 caused muscular atrophy by activating the NF-κB-inducing protein NIK. NIK is a type of enzyme called a kinase, and is essential for an NF-κB signalling pathway that is implicated in many chronic inflammatory diseases[9]. Tumour-bearing mice that were genetically engineered to lack EDA2R were protected against body-weight loss and muscle atrophy, but not from loss of fat mass, indicating that the EDA2 signalling axis mediates muscle loss during cancer-associated cachexia.

Bilgic and colleagues went one step further to elucidate how expression of the gene *Eda2r* is upregulated in skeletal muscle during cancer-associated cachexia. Of the proinflammatory cytokines that the authors tested, only OSM increased the expression of *Eda2r* in cultured myotubes. OSM is a member of the IL-6 family of cytokines, and signals through its receptor protein, OSMR (ref. 10). The authors found that levels of OSM were higher in blood-plasma samples from mice with cachexia than in samples from mice without cachexia, and showed that OSM can directly promote muscle atrophy. These effects were muscle-intrinsic, because ablation of *Osmr*, the gene that encodes OSMR, in skeletal muscle was sufficient to prevent the rise in expression of *Eda2r* and atrophy.

**"Improved mechanistic insights are urgently needed to support early diagnosis and better classification of people with cachexia."**

Bilgic and colleagues' findings reinforce the idea that chronic inflammation is a central mediator of tissue breakdown. Although this study suggests that targeting OSM and/or the EDA2 pathway might ameliorate muscle atrophy, several aspects will need to be considered for success in the clinic. For example, careful selection of patients in whom these inflammatory molecules are present might reveal individuals who could benefit most from the blockade of these mediators. The importance of identifying such individuals relates to the fact that these inflammatory pathways have various effects, and that different hierarchies of cytokine involvement presumably exist during the disease stages of pre-cachexia, cachexia and an advanced stage of cachexia termed refractory cachexia[3]. The study of these disease stages is currently limited by the lack of animal models that fully recapitulate the pathophysiological changes associated with the condition.

Because muscle loss and cachexia are found in a wide range of chronic inflammatory diseases, the various immune and metabolic contexts involved might provide different cachexia-promoting signals. Thus, improved mechanistic insights are urgently needed to support early diagnosis and better classification of people with cachexia. A 'magic bullet' that targets a single molecule to reverse cachexia-related muscle loss might not be around the corner[3]. Instead, physical exercise and nutritional interventions, together with pharmacological targeting of convergent hubs of inflammation, ideally taking into account organ-specific effects, will probably be the key to developing effective treatment for cachexia.

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1. Fearon, K. *et al. Lancet Oncol.* **12**, 489–495 (2011).
2. Baracos, V. E., Martin, L., Korc, M., Guttridge, D. C. & Fearon, K. C. H. *Nature Rev. Dis. Primers* **4**, 17106 (2018).
3. Argilés, J. M., López-Soriano, F. J., Stemmler, B. & Busquets, S. *Nature Rev. Clin. Oncol.* **20**, 250–264 (2023).
4. Cohen, S., Nathan, J. A. & Goldberg, A. L. *Nature Rev. Drug Discov.* **14**, 58–74 (2015).
5. Ferrer, M. *et al. Cell* **186**, 1824–1845 (2023).
6. Bilgic, S. N. *et al. Nature* **617**, 827–834 (2023).
7. He, N. & Ye, H. *Adv. Exp. Med. Biol.* **1228**, 255–267 (2020).
8. Orsso, C. E. *et al. J. Cachexia Sarcopen. Muscle* **13**, 1442–1459 (2022).
9. Sun, S.-C. *Nature Rev. Immunol.* **17**, 545–558 (2017).
10. Jones, S. A. & Jenkins, B. J. *Nature Rev. Immunol.* **18**, 773–789 (2018).

**The authors declare no competing interests.**
**This article was published online on 10 May 2023.**