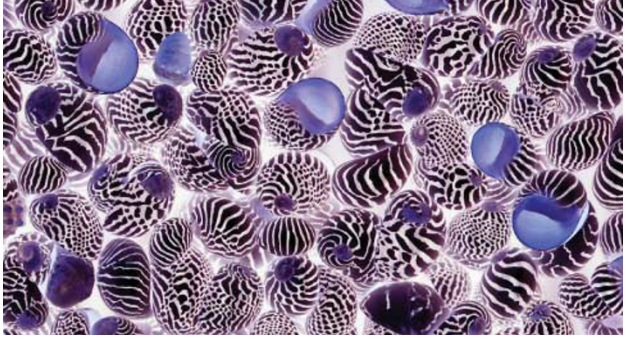

BIOINFORMATICS

The (computational) means and the motif

The identification of transcription-factor binding sites (TFBS) is essential for deciphering gene regulatory networks. But the complexity of tissue-specific gene regulation makes the identification of DNA-binding sites for unknown regulatory factors very tricky, particularly in vertebrates. Binding-site motifs that are involved in tissue-specific gene expression are common among the promoters of genes that are expressed in the same tissue, but not among promoters that control gene expression in other tissues. Michael Zhang and colleagues have developed a computational method that searches for highly degenerate TFBS motifs (and motif combinations) that are overrepresented in the promoters of tissue-specific genes, relative to genes that are not expressed in that tissue.

Degenerate motifs cannot adequately be described by a consensus sequence, so they are described instead by a scoring matrix, which indicates how often a specific nucleotide is found at a specific position within the motif. The researchers used an approach they called DME (discriminating matrix enumerator) to sequentially test each possible matrix and rank it according to how well it discriminates one set of promoters from another set (or how much the motif is overrepresented in one set of promoters relative to another).

Zhang and colleagues searched promoter sequences of vertebrate liver-specific genes, comparing a 'foreground' promoter set — the liver-selective promoter set (LSPS) of non-homologous promoters — with a 'background' vertebrate subset of promoters from the Eukaryotic Promoter Database (EPD), from which the promoters associated with liver had been removed. Reassuringly, many of the most overrepresented motifs they recovered were remarkably similar to those already known to bind to well-characterized liver-specific transcription factors. Likewise, when they searched for muscle-specific motifs, they found several that were similar to well-known muscle-specific TFBS.

The authors concluded that their method can accurately identify, or give a better description of, known TFBS, as well as previously uncharacterized motifs. However, they note that the choice of the background set used in this analysis needs to be guided carefully by the hypothesis being tested; the sequence properties of the chosen background set will influence the types of motifs picked up in the analysis. Nonetheless, the authors conclude that there is now sufficient sequence and expression data available for large-scale computational studies of tissue-specific TFBS, and that DME is sufficiently accurate to be used in such efforts.

Jenny Bangham

References and links

ORIGINAL RESEARCH PAPER Smith, A. D., Sumazin, P. & Zhang, M. Q. Identifying tissue-selective transcription factor binding sites in vertebrate promoters. *Proc. Natl Acad. Sci. USA* **102**, 1560–1565 (2005)

ETHICS WATCH

Cloned embryos: in search of criteria to determine their moral status

Recently, a new attempt was put to the United Nations to ban all human cloning, including therapeutic or research cloning. The advocates of this ban mainly based their position on the conviction that the human embryo has the same moral status as a person and should be treated with equal respect. But should the status of embryos or embryo-like entities that are generated by new technologies, such as somatic-cell nuclear transfer (SCNT), be considered with the same theories and principles as the status of embryos that are created by *in vitro* fertilization? These technologies raise a number of fundamentally new questions about the nature and moral status of embryos.

First, there is a classification problem: which entities should be classed as human embryos[1]? Traditional criteria, which include fertilization by human gametes, have to be abandoned as a necessary condition, because SCNT embryos are produced without fertilization. According to some, any cell from which a human being could, in principle, be created — even if assisted by sophisticated technology — should be regarded as a human embryo. However, this 'inclusive' definition implies that all somatic cells of a person's body have to be considered as (equivalent to) embryos — an untenable view. The urgency of the classification problem is highlighted by the production of hybrids through the transfer of a human somatic nucleus into an enucleated animal ooplast[2]. Some proponents argue that embryos created in this way are non-human because their mitochondrial DNA is non-human. Another criterium for a human embryo is that it has the potential to become a person, but this is challenged by the production of human parthenotes, which are created by the artificial activation of unfertilized eggs. Parthenotes cannot develop into full organisms and therefore do not fulfil the condition of potentiality.

Second, if these 'high-tech constructs' are considered to be human embryos, what about their moral status? In particular, the evidence indicates that embryos that are obtained by SCNT have a strongly reduced viability — what are the ethical implications of this? If this evidence is corroborated, research cloning would no longer be merely distinguished from reproductive cloning by the intention of the scientist. It might even be possible to design the SCNT technology to guarantee that, from the start, the embryo or embryo-like entity completely lacks the capacity to develop into a human being, like parthenotes. In this case, one of the main arguments in favour of respecting the human embryo — its potential to become a human being — would no longer be valid for embryos that are created by SCNT or parthenogenesis. This would also apply to certain categories of embryos that are created in the context of medically assisted reproduction[3]. With these points in mind, it is not obvious that all entities that are classified as embryos deserve the same respect.

As new techniques are being developed, we urgently need clarification of both the definition of the human embryo and the moral status of human embryos with limited viability. These questions need to be addressed in a continuing dialogue between scientists, ethicists and policymakers worldwide.

Guido Pennings and Guido M. W. R. de Wert
e-mails: Guido.Pennings@UGent.be; g.dewert@ige.unimaas.nl

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