from animal fats in recent human evolution[8]. Chimpanzees eat a small amount of meat, so it is not known what (if any) human-specific traits might have resulted from this deletion, but it does suggest that shifting dietary patterns could have been a feature of human evolution over long timescales.

Structural variation also seems to have had a role in brain evolution. Human brains are much larger than those of other apes, and it is plausible that genes involved in brain growth and development were key to the evolution of this trait. The authors analysed the sequences of genes that are active in radial glial cells, which are progenitors for neurons and other cells in the brain's cortex, and compared protein production by these genes in humans and chimpanzees using cortical organoids — 3D models of brain tissue grown *in vitro*. These analyses revealed that 41% of genes whose activity is suppressed in human radial glial cells are associated with a human-specific structural variant. Again, this is consistent with structural genomic changes causing disruption or loss of gene function during great-ape evolution.

Intriguing as Kronenberg and colleagues' findings are, there is also a broader significance to their work. Several groups and consortia are applying new sequencing technologies to different organisms. Ultimately, researchers want accurate, high-resolution assemblies for all species, and to compare these genomes on an equal footing. This will improve evolutionary analyses and reveal complex mutation processes that have hitherto been obscured. Large genome assembly currently remains hugely expensive, and even state-of-the-art sequencing tools struggle to resolve repetitive sequences on scales above a few hundred thousand base pairs, making assembly of certain genomes challenging. But tools to read whole genomes with negligible errors on inexpensive hardware are not far away, and are almost available for small bacterial genomes[9].

It is clear that we are leaving behind the initial period of evolutionary genomics, in which analyses involved comparing a genome of interest to a few 'gold standard' genomes, such as human, mouse or zebrafish. Instead, we are moving towards a more complete and equable genomic view of life. ■

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MEDICAL RESEARCH

Immune link to failure of cancer treatment

Prostate-cancer treatment usually fails after time as resistance to therapy develops. It emerges from studies of mice and human cells that a population of immune cells can cause this type of treatment resistance. SEE ARTICLE P.363

MATTHEW D. GALSKY

Prostate cancer causes more than 300,000 deaths annually worldwide and is one of the most common causes of cancer-linked mortality in men[1]. In 1941, the demonstration[2] that the condition regressed after surgical castration established a link between prostate-cancer growth and androgens — the hormones, such as testosterone, that are mainly generated in the testes and aid the development of male characteristics. The current standard treatment for advanced-stage prostate cancer is androgen depletion by chemical means. However, this almost invariably provides only a temporary halt to the disease. When cancer progression resumes despite low androgen levels, the condition is known as castration-resistant prostate cancer. On page 363, Calcinotto *et al.*[3] report that the action of immune cells can drive this type of treatment resistance. This discovery could pave the way to new therapeutic options, and illuminates our understanding of the spectrum of interactions in the prostate-cancer microenvironment.

The androgen receptor is a protein that can regulate gene expression. Androgen-deprivation therapy can lead to prostate-cancer regression because the absence of androgen-mediated signalling causes cancer cells to die or cease dividing[4,5]. The resulting decrease in tumour size is often monitored in the clinic by tracking a decline in the level of a protein called prostate-specific antigen (PSA). Although it was originally thought that castration-resistant prostate cancer arises through mechanisms that are independent of androgen-mediated signalling, certain observations have challenged that. PSA expression is regulated by the androgen pathway, and an increase in the level of PSA almost always accompanies the development of castration-resistant disease[6]. Moreover, clinical improvement can occur when people undergoing androgen-deprivation therapy are also given extra treatments that hamper androgen signalling[7].

A range of mechanisms underlying castration-resistant prostate cancer have been reported[8], and several causes probably contribute to disease progression in any given individual. The identification of mechanisms associated with disease progression has led to the development of associated treatments. For example, up to half of castration-resistant prostate cancers[9] are accompanied by an increase in the number of copies of the androgen-receptor gene. This, along with other clues suggesting that androgen-receptor expression correlates with disease progression, has stimulated the generation of drugs that can inhibit the androgen receptor[10]. Castration resistance can also occur through an increase in the expression of enzymes that synthesize androgens, and this discovery led to the development of drugs that inhibit androgen biosynthesis[11]. However, resistance to both these types of inhibitor can develop, so there is still a need for additional clinical strategies.

Calcinotto and colleagues investigated whether immune cells might aid the development of castration-resistant prostate cancer. They focused on an immune-cell population known as myeloid-derived suppressor cells (MDSCs), which includes monocytes and neutrophils that might be in an immature state of abnormal activation. MDSC presence is linked to poor prognosis for patients who have prostate cancer[12], although this connection has been attributed to the suppression of an anticancer immune response. Calcinotto *et al.* observed that tumour biopsies from people who have developed castration-resistant prostate cancer contain more MDSCs that express the proteins CD11b, CD33 and CD15 than do samples from people whose prostate cancer has not progressed to the castration-resistant stage.

The authors investigated whether MDSCs might contribute directly to castration resistance, using human cell samples and mouse models of prostate cancer. In mice, the authors found that surgical castration resulted in an increase in the recruitment of MDSCs to tumours, compared with the recruitment observed in control animals given a mock operation. Calcinotto and colleagues grew mouse MDSCs *in vitro* and isolated samples of the culture medium. When this medium was added to androgen-dependent

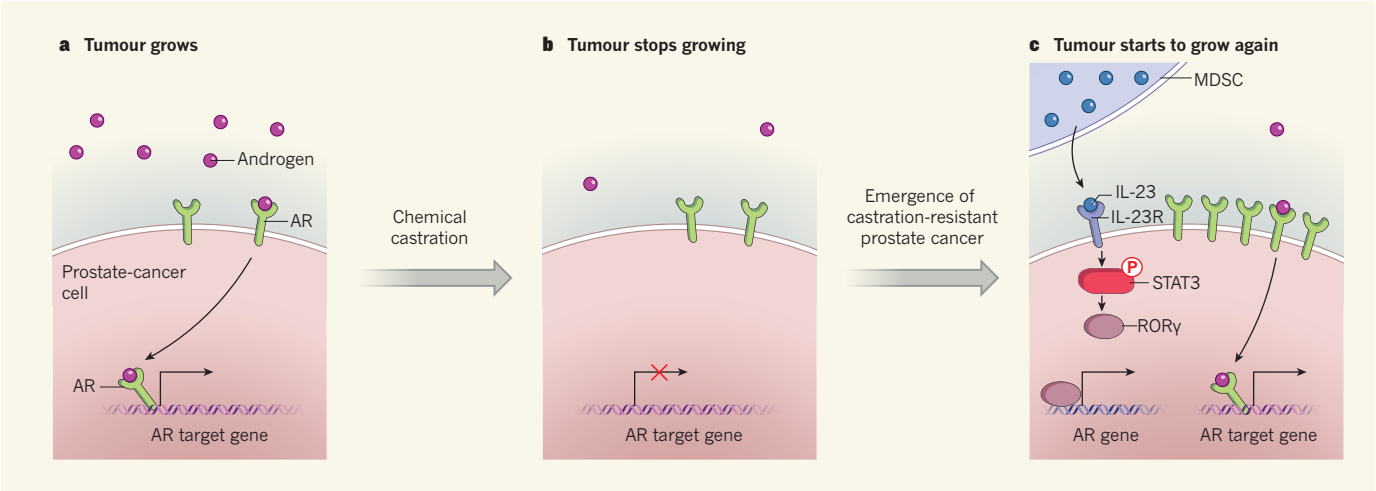

Figure 1 | An immune cell drives treatment resistance in prostate cancer. Calcinotto *et al.*[3] used mouse models and human clinical samples to investigate how prostate cancer evades therapy. **a**, If male hormones called androgens bind to the androgen receptor (AR), this can drive the expression of genes that promote prostate-cancer growth. **b**, A standard treatment for the disease is chemical castration, in which drugs are used to decrease androgen levels. However, the subsequent slowing of tumour progression is not permanent. **c**, When tumour growth returns, the condition is called castration-resistant prostate cancer. Calcinotto and colleagues found that a type of immune cell called a myeloid-derived suppressor cell (MDSC) can cause this treatment failure. If an MDSC cell secretes a protein called IL-23, this might bind to the IL-23 receptor (IL-23R) on tumour cells. This binding triggers a pathway in the tumour cell mediated by the proteins RORγ and STAT3 (the latter is phosphorylated; P is a phosphate group), which can drive AR expression. This increase in AR expression helps to drive the androgen-dependent gene expression that boosts prostate-cancer growth.

prostate-cancer cell lines cultured *in vitro* under androgen deprivation, it sustained the proliferation and survival of the cells and caused an increase in the transcription of genes whose expression is driven by the androgen receptor.

The authors carried out equivalent experiments using human cells and made similar findings. Furthermore, the use of pharmacological techniques to deplete MDSCs delayed the emergence of castration resistance in mice. Together, these results suggest that MDSCs secrete a factor that drives the emergence of castration-resistant prostate cancer.

To identify this key factor, the authors took samples of tumours and associated cells from castrated mice and from animals that underwent a mock operation, and searched for the genes that showed the greatest increase in expression in the samples from castrated mice. Their results included the gene encoding IL-23 (an immune signalling protein called a cytokine) and a gene that encodes a subunit of the receptor to which IL-23 binds. Analysis of prostate-cancer specimens from the clinic confirmed the importance of IL-23, and there were more IL-23-expressing MDSCs in castration-resistant prostate-cancer specimens than in specimens from tumours that were not castration resistant.

Calcinotto and colleagues propose that signalling mediated by MDSC-secreted IL-23 and by the IL-23 receptor on prostate-cancer cells promotes the development of castration-resistant prostate cancer. Using pharmacological or genetic approaches to block IL-23-mediated signalling in mice, they obtained evidence that such treatment delays the development of castration-resistant prostate cancer.

The authors carried out studies to determine the signalling pathway downstream of IL-23 that mediates the return of tumour growth, and focused on two IL-23-regulated proteins (STAT3 and RORγ) that are part of a pathway that boosts androgen-receptor signalling[13]. Their results are consistent with a model in which IL-23-mediated activation of the STAT3–RORγ pathway leads to an increase in expression of the androgen receptor and an increase in expression of genes whose transcription depends on that receptor (Fig. 1). Strikingly, the authors demonstrated that if mice that had developed castration-resistant prostate cancer were given an antibody that blocks IL-23 and an androgen-receptor inhibitor called enzalutamide, this reversed castration resistance and caused the animals' tumours to shrink.

Calcinotto and colleagues' work has important clinical implications and advances our understanding of the biological processes that underlie castration resistance. Antibodies that block IL-23 are approved for clinical use to treat autoimmune conditions, which clears the way for them to be tested as a possible treatment for castration-resistant prostate cancer. The findings also raise the question of whether immune cells might contribute to the progression of other sorts of cancer in which growth is driven by hormone-receptor signalling. Some controversy currently exists about whether MDSCs are a cell population that is distinct from normal neutrophils and monocytes, given that MDSCs are highly similar to those cells, yet are considered functionally different. There is not yet a clear consensus about how to identify MDSCs on the basis of the expression of cell-surface markers[12]. This issue could affect future studies of these cells.

As with any disease mechanism studied mainly in animal models, the prevalence of possible MDSC-associated castration resistance in humans remains to be determined. It might be a minor mechanism in most patients, a major mechanism in a minority of patients or somewhere in between. The scale of the effect of MDSCs, and the ability to select the specific people likely to respond to treatment targeting castration-resistant tumours, will probably be crucial in determining whether such therapy against prostate cancer is successfully implemented in the clinic. ■

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