50 Years Ago

The emphasis on eugenics as the point of application of molecular biology overlooks the most immediate prospects for the understanding and then control of human development. To dramatize the antinomy, I propose the term 'euphenics' as the counterpart of 'eugenics' in the same sense that 'phenotype' is opposed to 'genotype' … Man's control of his own development, 'euphenics', transmutes the means, and also the ends of eugenics, as have all the precedent cultural revolutions that have shaped the species: language, agriculture, political organization, the physical technologies.
From *Nature* 4 May 1963

100 Years Ago

Practical men are at length beginning to realise that the utilisation of the store of potential energy in coal by more rational methods than have hitherto prevailed is a problem that has to be grappled with seriously if our supremacy in the chief manufactured products of the world is to be maintained … Enormous economies might be effected if more scientific—that is, more common-sense—methods were employed in the consumption of coal … It has been calculated that our annual consumption of coal is from 143 to 168 million tons per annum, of which from 30 to 36 million tons are used for domestic purposes. Of this huge amount it is estimated that from 40 to 60 million tons are practically wasted … The subject, indeed, is admittedly of national importance, but the fear is that this country will only waken up to the full significance of that fact when the pinch of necessity has tightened to a real grip—so tight, indeed, that it will be too late to shake it off.
From *Nature* 1 May 1913

lie close to the substrate phosphorylation site before guiding it into the mTOR active site. The authors suggest that this two-part substrate-recruitment mechanism facilitates substrate selectivity and entry into the otherwise restricted catalytic site. It might also provide an additional layer of regulation to ensure that mTOR does not inappropriately phosphorylate non-physiological substrates that do not possess a TOS motif and an FRB-binding domain.

In cancer cells, several mutations that hyperactivate mTOR have been identified in the FAT domain and its interface with the kinase domain[5]. Yang and colleagues argue that these mutations cluster to regions that control substrate access and loosen the structural skeleton, including the FRB domain, which otherwise restricts substrate admission to the active site.

There are more than 250 clinical trials in progress or planned to evaluate the efficacy of diverse mTOR inhibitors as anticancer agents[6]. Yang *et al.* have crystallized mTOR with a highly specific inhibitor (Torin2), as well as with two other, less selective compounds[7] (PP242 and PI-103). These compounds bind and inhibit mTOR in markedly different ways, providing a wealth of information on features of the mTOR active site that will undoubtedly be exploited to develop even more potent and selective inhibitors.

Previous work[8] showed that the complete mTORC1 complex is a dimer with a striking empty central cavity, which was proposed to facilitate substrate access. The same paper also found that rapamycin treatment caused disassembly of mTORC1 subunits. The current study provides no insight into how kinase activity and substrate phosphorylation would be affected by mTORC1 dimerization, nor does it suggest how rapamycin could induce complex disassembly.

Further work is also required to uncover why rapamycin does not inhibit mTORC2. Also, much remains to be understood about how RAPTOR and RICTOR sense the diverse upstream signals that continuously bombard mTOR complexes, and how this information is coupled to mTOR activation and substrate access to its active site. Fruitful knowledge is to be gained from research in this area, especially from structural analysis of even larger mTOR fragments in complex with other subunits. ■

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IMMUNOLOGY

Memory cells sound the alarm

In a finding that could have implications for vaccine design, memory immune cells at mucosal surfaces have been shown to respond to encounters with pathogens by issuing signals that recruit other memory cells to the site.

JENNIFER E. SMITH-GARVIN & LUIS J. SIGAL

The immune system clears pathogens it has encountered before more efficiently than those of an initial infection because specialized cells, known as memory cells, can remember and rapidly eliminate them. This process is the bedrock of all vaccines. Writing in *Nature Immunology*, Schenkel *et al.*[1] show that, in mice, a small number of memory cells that reside near sites of pathogen entry sound an alarm that recruits more memory cells from the blood to rapidly boost defences at the front line of a subsequent infection.

Most infections are initiated by pathogens that breach epithelial surfaces, such as the skin and the mucous membranes that line the genital, respiratory and gastrointestinal tracts. The immune system responds through the orchestrated actions of innate and adaptive immune cells. Innate cells are distributed throughout the body in large numbers; they can immediately identify and respond to pathogens, but they lack specificity and often fail to control an infection on their own. However, the B cells and T cells of the adaptive immune system have surface receptors that allow them to respond in a specific manner; they also have diverse mechanisms to eliminate infections. For example, in the case of $CD8^+$