Biology, Clinical Translation in Renal Cell Carcinoma

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Description

Improvements in health care, sanitation, diet, and education over the past century have markedly increased life expectancy, but this has not been paralleled by concomitant increases in healthy life expectancy. Increasing health span, which is the time spent free of major illness or disease, is therefore an important priority worldwide. The UK Government, for example, has pledged to increase the healthy life expectancy of the UK population by an extra 5 years by 2035 without increasing inequality.

Renal Cell Carcinoma

Targeted therapies and immune checkpoint inhibitors have advanced the treatment landscape of Renal Cell Carcinoma (RCC) over the last decade. While checkpoint inhibitors have demonstrated survival benefit and are currently approved in the front-line and second-line settings, primary and secondary resistance is common. A comprehensive understanding of the mechanisms of immune evasion in RCC is therefore critical to the development of effective combination treatment strategies. This article reviews the current understanding of the different, yet coordinated, mechanisms adopted by RCC cells to evade immune killing; summarizes various aspects of clinical translation thus far, including the currently registered RCC clinical trials exploring agents in combination with checkpoint inhibitors; and provides perspectives on the current landscape and future directions for the field.

Application of the experimental design of genome-wide association studies is now 10 years old (young), and here we review the remarkable range of discoveries it has facilitated in population and complex-trait genetics, the biology of diseases, and translation toward new therapeutics. We predict the likely discoveries in the next 10 years, when GWASs will be based on millions of samples with array data imputed to a large fully sequenced reference panel and on hundreds of thousands of samples with whole-genome sequencing data.

Achieving this goal would simultaneously improve individual quality of life, increase productivity, and boost national wealth. Notably, a gain of just one additional healthy year is predicted to be worth US$38 trillion to the USA. However, a 2021 review of national progress in the UK towards this goal revealed that policy makers have little confidence that healthy life expectancy can be markedly improved either through focusing on technological solutions or on diet and exercise regimes.

The same review revealed a general lack of awareness and scrutiny of the potential offered for improving health in later life by ameliorating the ageing process itself. This unawareness is alarming when set against the backdrop of a quiet research revolution in biogerontology that has seen the identification of some key hallmarks of ageing, evidence that these hallmarks and underlying mechanisms independently predict the emergence of age-related diseases in real patients, and positive outcomes from preclinical and early-stage human clinical trials based on targeting ageing mechanisms. Humanity stands on the threshold of being able to prevent multimorbidity and age-associated diseases by addressing the underlying biology of ageing; parallels with the era of antibiotics do not seem unduly hyperbolic.

Androgen Receptor

More specifically, activation of the Androgen Receptor (AR) signaling emerges as the key oncogenic pathway. SPOP-mutant prostate cancer patients respond to AR inhibition in various clinical settings. Molecular insights on how mutant SPOP promotes tumorigenesis may open more specific therapeutic avenues which, in combination with conventional AR-targeting agents, could improve the outcome of patients with SPOP-mutant prostate cancer.

Ignorance of these developments carries appalling costs, which have been, and will continue to be, borne by older people unless the situation changes. For example, the UK's 2017 healthy ageing grand challenge specifically excluded biomedical science research from its funding remit, and the extensive decade of healthy ageing: Baseline report by WHO, fails to mention these advances, or even the word biology, focussing instead on socioeconomic determinants of health and overcoming ageism. Given that hallmark ageing mechanisms cause the progressive failure of innate and adaptive immunity, it is a fascinating counterfactual to consider how the ongoing COVID-19 pandemic would have been handled had it been preceded by a sustained

international effort to target immune senescence and enhance later life immune function. The need to avoid such mistakes in the future is patent, as are the triple economic benefits that will accompany efforts in this area.

It is perhaps the perceived complexity of ageing biology that has dissuaded policy makers from directly tackling it. As a result, academic research on ageing in many parts of the globe is fragmented and siloed, and driven by funding models and professional metrics that reward specialisation and disease-specific focus. However, the biological mechanisms that cause ageing must be a central focus if integrational and intersectional approaches aimed at improving lifelong health are to be truly effective.

Comprehensive cancer genome studies have revealed genetically-defined subtypes of prostate cancer with distinct truncal driver mutations. Because prostate cancer has been largely seen as a rather uniform disease, the clinical significance of this discovery remained largely obscure. However, recent findings imply distinct biological features and therapeutic vulnerabilities linked to specific truncal mutations. Here we review our current understanding of prostate cancers harboring recurrent point mutations in the ubiquitin ligase adaptor protein SPOP and discuss opportunities for future clinical translation.