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What dictates tumour cell sensitivity to exercise?

With great interest, we have read the Perspective article by Fiuza-Luces et al.[1] on exercise-induced anticancer immunity. The authors highlighted a well-known theory that exercise-induced immunosurveillance — with a prominent role for natural killer (NK) cells — may underpin the anticancer effects of physical activity in humans. It is worth stressing that although epidemiological evidence suggests that physical activity reduces the risk of a cancer diagnosis and cancer mortality, this differs between cancer types[2,3]. Also, earlier disease stages may be less susceptible than later stages — for example, a higher physical activity level reduces the risk of prostate cancer mortality[3], but not a prostate cancer diagnosis[2].

Preclinical studies indicate that both natural killer (NK) cells and T cells are integral to the anticancer effects of exercise[1,4], and a likely reason for the variable efficacy of physical activity may lie in the fact that cancer clones differ in their sensitivity to immune effector cells such as $CD8^+$ T cells and NK cells. For example, physical activity is largely ineffective in reducing the risk of human cancers that are known to have a low tumour mutational burden[2,4,5] and therefore low tumour neoantigen presentation[6].

With regards to NK cells, it was shown that exercise preferentially mobilizes highly differentiated NK cells with a cytotoxic phenotype in a process that is dependent on exercise intensity and duration[7,8]. Fiuza-Luces et al.[1] discuss a landmark study by Pedersen et al.[9] that suggested a mechanistic link between regular exercise, NK cells and tumour growth in mouse cancer models. However, we would like to emphasize that evidence in support of a specific effect of exercise on the anti-tumour properties of NK cells remains limited to preclinical or in vitro human cell line studies using tumour cells that are sensitive to NK cells[8,9], thus rendering these tumours overtly susceptible to the immune stimulus of exercise. So far, the effects of exercise on cancer have only been tested in three pilot randomized controlled trials in patients with early-stage prostate cancer[10–12]. All of these studies failed to show exercise-induced NK cell infiltration into tumour tissue in exercised patients compared to non-exercised controls. These collective null findings are unsurprising given the poor sensitivity of early-stage prostate cancer to immune effectors[2,4,5].

We hope that the Perspective article by Fiuza-Luces et al.[1], and the considerations added in this Correspondence, stimulate research to investigate why physical activity is effective in reducing the outgrowth of some but not all cancers in humans. Tumour sensitivity to T cells and NK cells may dictate this efficacy, and it is likely that other immune effectors and mechanisms are also involved. Ultimately, progress in exercise oncology will require continued integration and careful interpretation of epidemiology, preclinical and clinical research to facilitate evidence-based progress in the field.

John P. Campbell[1,2], David Walzik[3] & Philipp Zimmer[3]

[1]Department for Health, University of Bath, Bath, UK. [2]School of Medical and Health Science, Edith Cowan University, Joondalup, Australia. [3]Division of Performance and Health (Sports Medicine), Institute for Sport and Sport Science, TU Dortmund University, Dortmund, Germany.

e-mail: philipp.zimmer@tu-dortmund.de

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Competing interests

The authors declare no competing interests.