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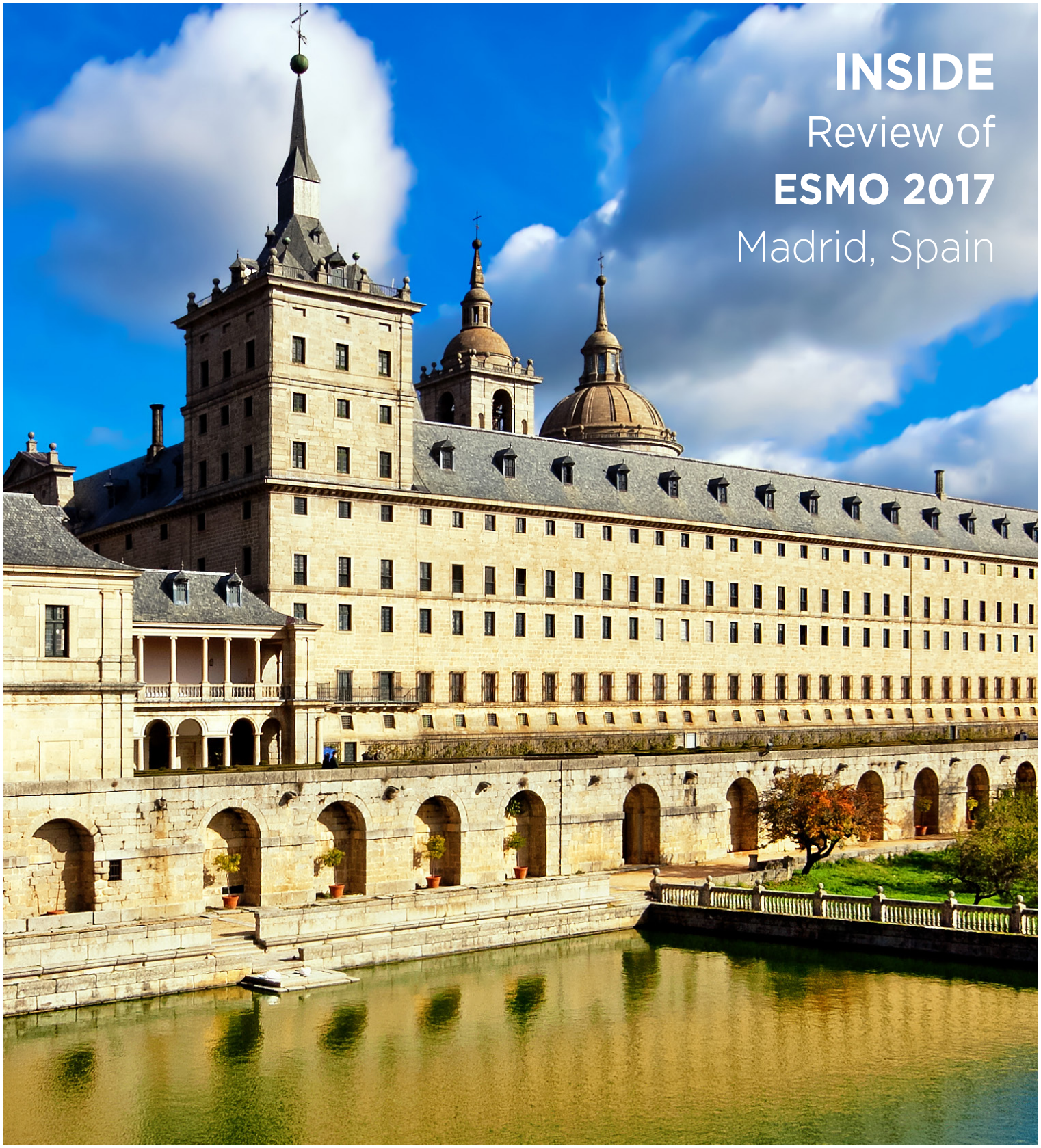

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SIGNAL TRANSDUCTION PATHWAYS REGULATING ALTERNATIVE SPLICING OF TUMOUR-RELATED RAC1B

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The expression of most genes in the human genome can yield >1 transcript through the process of alternative splicing of pre-messenger RNA. Alternatively spliced transcripts significantly increase the complexity of human gene products because they either influence transcript degradation levels or encode functional protein variants that differ in specific domains.[1] Even with cutting-edge transcriptomic approaches, it has been extremely challenging to understand or predict the complex splicing patterns observed in tissues or in diseases such as cancer; therefore, a better understanding of how cells are able to regulate alternative splicing is required.

Our group previously characterised the molecular mechanisms regulating RAC1b, an alternative splice variant that is overexpressed in colorectal tumours. RAC1b displays altered activation and downstream signalling properties and is required for colorectal cancer cell survival.[2] The method used by tumour cells to enhance this alternative splicing event remains largely unknown.

Alternative splicing is regulated through the binding of splicing factors to gene-specific sequence elements and can be modified by changing either the expression levels of competing factors, or their activity and subcellular localisation, through protein phosphorylation.[3] The study of RAC1b revealed that two antagonistic SR protein-family splicing factors, SRSF1 and SRSF3, bind to regulatory sequence elements in the alternative exon and determine the rate of exon inclusion. While the inhibitory factor SRSF3 was found to be regulated at the

transcriptional level, the antagonistic SRSF1 was regulated through protein phosphorylation.[4] Interestingly, recent data revealed that colon epithelial cells increase RAC1b expression in an inflammatory environment, indicating the role of cytokine signalling as an upstream event that is necessary for changes in alternative splicing.[5] Here, we explore how signalling pathways are involved in the deregulation of alternative RAC1b splicing in colorectal tumour cells.

Using HT29 cells that represent serrated colorectal tumours, with both the *BRAF* gene mutation Val600Glu in one allele and RAC1b overexpression, we depleted 20 candidate splicing-regulatory protein kinase genes by RNA interference. It was found that AKT2, AKT3, GSK3β, and SRPK1 are all required to sustain RAC1b levels. While knockdown of AKT2 and AKT3 affected only RAC1b protein levels, suggesting a post-splicing effect, the depletion of GSK3β or SRPK1 decreased RAC1b alternative splicing, an effect mediated through changes in splicing factor SRSF1. In particular, the knockdown of SRPK1, or pharmacological inhibition of its catalytic activity, reduced phosphorylation and subsequent translocation of SRSF1 to the nucleus, limiting its availability to promote the inclusion of alternative exon 3b into the RAC1b pre-messenger RNA.[6] This regulatory pathway was also found to be controlled by GSK3β. Interestingly, GSK3β phosphorylation was identified as a target of the anti-inflammatory drug ibuprofen, which inhibits RAC1b overexpression.

This work advances the current research on aberrant splicing events in cancer and demonstrates that oncogenic signal transduction pathways deregulate alternative splicing. Moreover, our results show that alternative splicing may be drug revertible and promote exploitation of the growing list of kinase inhibitors as a therapeutic resource to correct splicing in cancer cells.

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IDEAL CARDIOVASCULAR HEALTH IN PATIENTS WITH A RECENT DIAGNOSIS OF COLORECTAL CANCER

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Keywords: Ideal cardiovascular (CV) health, cancer survivors, cardiovascular (CV) risk factors, colorectal cancer, physical activity, healthy lifestyle.

Colorectal cancer survivors have an elevated risk of comorbid disease, particularly cardiovascular (CV) disease, due to both the age at diagnosis (around 60 years) and shared lifestyle risk factors; namely, being overweight/obese, physical inactivity, poor diet, and smoking.[1,2] BMI is the strongest correlate of comorbid CV disease in cancer survivors.[2] Comorbid chronic conditions can have