

Editorial

Editorial for Special Issue “Molecular Mechanisms and Signaling Pathways in Melanoma”

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Melanoma represents the leading cause of death from cutaneous malignancy [1], despite the development and deployment of novel targeted therapies (BRAF and MEK inhibitors) and immunotherapy [2]. Indeed, these treatment regimens are often short-lived and, despite being initially effective, are frequently followed by relapse.

Melanomagenesis and melanoma tumor progression are multistep processes, involving several cellular mechanisms and intracellular signaling pathways. One of the leading signaling pathways involved in melanoma is the MAPK signaling pathway, as exemplified by the leading driver mutations in the *BRAF*, *NRAS*, and *NF1* genes, as well as the involvement of receptor tyrosine kinases, such as KIT [3]. Thus, the exploration of these and other molecular mechanisms may help in uncovering new drug targets or potential drug combinations to be tested in clinical trials, with the aim of achieving FDA approval for routine treatment.

For this Cancers Special Issue, we collected relevant review articles and original research articles that summarize our current knowledge and advance our understanding of the pathogenesis of, and target therapies for, melanoma.

Among the receptor tyrosine kinase family, MET, the receptor for hepatocyte growth factor (HGF), has emerged as a potential key player in melanoma [4]. In their article, Song et al. [5] highlight how MET inhibition with selective kinase inhibitors appears to influence the expression of the checkpoint protein PD-L1 through interference in the JAK-STAT signaling pathway. Moreover, a physical integration between MET and PD-L1 has been demonstrated, both via co-immunoprecipitation experiments and through co-localization immunofluorescence studies. This interplay offers the theoretical opportunity to target these proteins with a combination cocktail that utilizes selective inhibitors of these surface receptors.

As mentioned above, *NRAS* represents one of the main molecular drivers in melanoma but, unfortunately, no FDA-approved drugs directly targeting *NRAS* mutations are currently available. Banik et al. [6] have now demonstrated that p38 has a selective tumor-suppression capability in *NRAS*-mutated melanoma, as it alters the actin cytoskeleton and autophagy-related targets. These findings open up opportunities to indirectly target the *NRAS* pathway with drugs modulating these proteins.

By using an RNA-sequencing strategy in conjunction with ChIP-seq techniques on melanoma cell lines with a high expression of GLI1-3 proteins in the hedgehog signaling pathway, Kurtovic et al. [7] were able to validate 21 targets via subsequent quantitative PCR. These proteins may represent potential targets for therapy, although they require further validation.

Two reviews within this Special Issue look into different and less-explored aspects of melanoma. Ye et al. [8] discuss the role of exosomal miRNAs in melanoma progression, by looking at their influence on metastasis, immune escape, and the tumor microenvironment.



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While this is an unconventional route to take in targeting melanoma, it may prove to be a viable alternative to current therapeutic regimens.

Finally, Pagliuca et al. [9] detail recent findings on melanoma tumor cell plasticity and phenotypic switching, noting that these important features are now recognized as hallmarks of cancer. Tumor plasticity appear to be regulated at the epigenetic level, and a debate continues on whether this feature is acquired through a selection process during tumorigenesis or pre-exists within the tumor in the early stages. Regardless, tumor plasticity represents another unconventional target that future research will, hopefully, allow us to include in our therapeutic toolbox.

Overall, novel therapeutic strategies are on the horizon for melanoma, and drug combinations appear to represent the most logical and rational approach to helping patients overcome ineffective treatments or treatment resistance, to ultimately improve survival and quality of life.

Conflicts of Interest: The authors declare no conflict of interest.

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