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Biology of MPM

The pathologic profile of MPM (malignant pleural mesothelioma) is far from straightforward, making diagnosis and prognosis difficult.

Inhalation of asbestos fibres is known to promote an inflammatory response. Over time, this can lead to malignant transformation via multiple mechanisms, including:[1]

- Generation of reactive oxygen species and reactive nitrogen species leading to DNA damage
- Accumulation of carcinogens that are absorbed by the asbestos fibres themselves
- The release of inflammatory cytokines and growth factors

Perhaps reflecting this multifaceted pathogenesis, MPM tumours often show a high degree of intratumoural heterogeneity (variations within the same tumour). This feature may partly account for the observation that they quickly become resistant to systemic therapy.[1]

Are biomarkers used to inform treatment decisions in MPM?

Use of biomarkers in the clinic has so far been extremely limited. Although a serum, mesothelin assay, has been approved by the US Food and Drug Administration (FDA),[2] serum levels of soluble mesothelin have variable utility in diagnosis and in ascertaining treatment response and prognosis.[3-5] A recent meta-analysis did not identify a single serum or pleural fluid biomarker that could be recommended for routine clinical practice.[4]

Currently, there are no validated biomarkers for screening people who have been exposed to asbestos for MPM,[3] although research is ongoing and earlier diagnosis may have considerable impact on the course of disease.[1] There is also a pressing need to identify and validate biomarkers to guide the development of new therapies in MPM or to inform patient selection for specific treatments.

Driver mutations

With the possible exception of BAP1, no driver mutations have been identified.[1] Even then, although BAP1 occurs in 47–67% of MPM tumours, the mechanism by which it is involved in malignant transformation has yet to be firmly established.[7]

Further research has shown that the genetic alterations in MPM tumours mostly occur in the p53/DNA repair pathway, the cell cycle, the mitogen-activated protein kinase pathway and the phosphoinositide 3-kinase (PI3K)/AKT pathway.[8] These pathways may therefore warrant further research to investigate novel targeted treatments in MPM.

References

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