Preface

Neurofibromatosis type 1 is a common autosomal dominant cancer predisposition syndrome that is caused by germline mutations in the \textit{NF1} tumour suppressor gene. The aim of this volume is to present in concise fashion, but as comprehensively as possible, current knowledge of the molecular genetics and cellular biology of neurofibromatosis type 1 (NF1). The molecular and cellular biology of NF1 is a burgeoning subject with a large and widely dispersed literature that is difficult to access. This volume comprises 43 chapters, written by internationally recognised experts in the field, on the latest developments in the molecular and cellular biology of NF1. It should be of interest to human geneticists, clinicians, general practitioners, psychologists and genetic counsellors as well as undergraduates and postgraduates in medicine and the biological sciences. It is hoped that this volume will serve as a useful reference source for years to come.

Since the publication of our first edited volume on the topic in 1998 (Upadhyaya and Cooper 1998), there has been an explosion in our knowledge of the molecular and cellular mechanisms underlying the development of the different features of NF1. During this period, remarkable advances have been made in the management of NF1 clinics, molecular diagnosis, the detection of somatic mosaicism, genotype–phenotype correlations, and the identification of \textit{NF1} modifying loci. Intensive research over the last 14 years has greatly expanded our understanding of the functional role of the \textit{NF1} gene and its protein product (neurofibromin), the germline and somatic mutational spectra of the gene and the underlying mutational mechanisms. An apparent relationship between \textit{NF1} and mismatch repair genes has also been explored.

With the emergence of sensitive imaging techniques, including whole-body MRI and PET studies, a wealth of information on the load of internal tumours and their management has been generated. We have also acquired a greatly improved understanding of bone skeletal and cardiovascular abnormalities in NF1 patients. Clinical, molecular and cellular aspects of cognitive impairment have been extensively studied, giving rise to therapeutic possibilities and spawning clinical trials.

Much has been learnt about the pathogenesis of the different types of NF1-associated tumours including optic gliomas, phaeochromocytomas, cutaneous
and plexiform neurofibromas, malignant peripheral nerve sheath tumours (MPNST), glomus tumours and leukaemia. As a result, we are better equipped in terms of our ability to manage these tumours. Identification of the cell(s) of origin of NF1-associated tumours will be important for the design of new therapies. Available evidence suggests that cutaneous neurofibromas arise from skin-derived precursors or their derivatives, whereas bi-allelic inactivation of \( \text{NF1} \) in the Schwann cell lineages leads to plexiform neurofibroma formation. The cell of origin of MPNSTs is not yet known.

We also remain ignorant of the mechanisms underlying the transformation of benign neurofibromas to malignancy. These may involve sequential events involving both genetic and epigenetic alterations, and the order in which these changes occur needs to be elucidated. The tumour microenvironment is now known to play a critical role in NF1 tumorigenesis and this will need to be further explored. Beyond its central role in NF1, the \( \text{NF1} \) gene is also emerging as an important tumour suppressor gene in its own right in sporadic cancers.

We have learned a lot about the biology of NF1 from animal models including \textit{Drosophila}, zebrafish and mouse. These models are helping to advance our knowledge of disease progression and should facilitate the identification of biomarkers, the development of suitable therapies, and the prediction of drug response in clinical trials. Research based on preclinical work has already been translated into therapeutic trials for various NF1 features including plexiform neurofibromas, gliomas, MPNST and neurocognitive disorders. A new class of human developmental syndromes, designated “RASopathies”, has recently been recognised that are caused by germline mutations in different genes involved in regulating the Ras/MAPK signalling pathway. Indeed, locus heterogeneity is evident in NF1: one of the RASopathies, Legius syndrome, is caused by mutations in the \( \text{SPRED1} \) gene and has clinical features that overlap with NF1.

Recent reports have indicated that different cancers may be associated with different patterns of micro-RNA (miRNA) expression pattern, and these might provide us with extra prognostic and diagnostic markers, as well as providing new avenues for therapeutic intervention in MPNSTs. Indeed, a subpopulation of cells positive for CD133 (a cancer stem marker) have been detected in human primary MPNST. Functional analyses have confirmed these cells to be cancer stem cells (CSC) and they have been shown to exhibit enhanced chemo-resistance in vitro (Borrego-Diaz et al. 2012).

Worldwide NF1 lay foundations, which provide an important resource for the NF1 community, are also emerging as drivers of NF1 research. A comprehensive account of social problems faced by NF1 sufferers is discussed. Finally, potential future directions for NF1 research are discussed, highlighting novel research avenues and therapeutic targets.

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References


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