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BRAF mutations in melanoma and colorectal cancer: A single oncogenic mutation with different tumour phenotypes and clinical implications

F. Sclafani [a,*], G. Gullo [a], K. Sheahan [b], J. Crown [a]

[a] *Medical Oncology Department, St. Vincent's University Hospital, Dublin, Ireland*
[b] *Pathology Department, St. Vincent's University Hospital, Dublin, Ireland*

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Contents

Abstract

BRAF is an oncogene encoding a serine–threonine protein kinase involved in the MAPK signalling cascade. BRAF acts as direct effector of RAS and through the activation of MEK, promotes tumour growth and survival. Approximately, 8% of cancers carry a BRAF mutation. However, the prevalence of this mutation varies significantly across different tumour types.

There has been increasing interest in the specific role of BRAF mutations in cancer growth and progression over the last few years, especially since the clinical introduction of therapeutic BRAF inhibitors.

In this paper we review the published literature on the role of BRAF mutations in melanoma and colorectal cancer, focusing on similarities and differences of BRAF mutations with respect to frequency, demographics, risk factors, mutation-associated clinico-pathologic and molecular features and clinical implications between these two diseases.

Keywords: BRAF mutation; Biomarkers; Genotype; Histotype; Melanoma; Colorectal cancer; BRAF inhibitors

* Corresponding author at: Medical Oncology Department, St. Vincent's University Hospital, Elm Park, Dublin, Ireland.
Tel.: +353 1 221 3443; fax: +353 1 221 5023.
E-mail address: dr.sclafani@gmail.com (F. Sclafani).

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1. Introduction

Over the last two decades, a body of knowledge on the complex intracellular mechanisms promoting cancer initiation and progression has become available. As a result, new biologically targeted agents have been developed and introduced into clinical practice. However, due to the complexity of tumour signalling pathways, the tumourigenic potential of some mutations has not always been immediately recognized. In addition, the relationship between targeted therapies, tumour targets and predictive biomarkers has sometimes been complex and unpredictable.

In the early 1980s, RAF was first identified as a retroviral oncogene encoding a serine–threonine protein kinase and promoting the development of tumours in mice and chickens [1,2]. Conversely, the role of RAF in human tumours was originally restricted to its involvement in the MAPK cascade. RAF was then assumed to act as an effector of RAS and BRAF was found to be more active than the other members of the RAF family [3] (Fig. 1).

The report by Davies et al. [4] on the presence of BRAF mutations in human malignancies, prompted increased interest in the role of this protein kinase in cancer growth and progression.

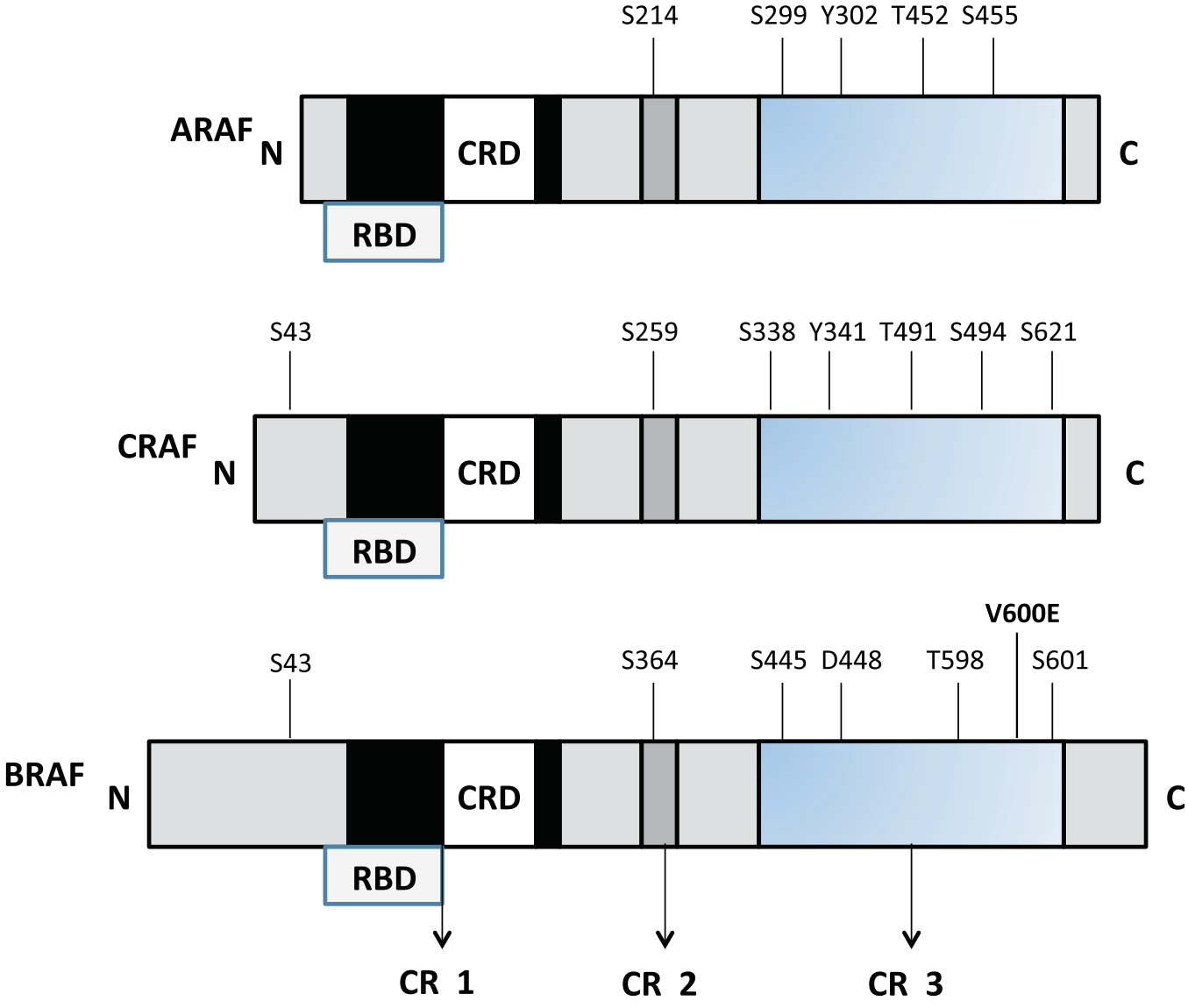

Fig. 1. Domain structures and phosphorylation sites of the three RAF family members. ARAF, CRAF and BRAF share three conserved regions. The N terminal lobe contains the glycic loop and the C terminal lobe contains the activation segment. Each RAF family member has several conserved regulatory phosphorylation sites. Some are inhibitory phosphorylation sites (i.e., S43, S259 and S621 in CRAF, S364 in BRAF). Some others are activating phosphorylation sites (i.e. S338, Y341, T491, S494 in CRAF, S445, D448, T598, S601 in BRAF). The BRAF V600E mutation is located in the activation segment and activates constitutively the B-RAF kinase activity mimicking the RAS-induced phosphorylation of native B-RAF at threonine 598 and serine 601. Abbreviations: RBD, RAS binding domain; CRD, cysteine-rich domain; and CR, conserved region.